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STUDIES ON THE NATURE OF PAIN ARISING FROM AN ISCHEMIC LIMB

I. CLINICO-EXPERIMENTAL OBSERVATIONS

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OVER a decade has passed since Lewis, Pickering, and Rothschild[1] showed that interference with the blood supply of an actively exercising limb soon stopped the effort because of the development of unbearable muscular pain. Since then, further observations by Lewis[2] and other investigators,[3, 4] not all of whom have been in accord, have added to our knowledge of ischemic pain. In our attempt to solve the basic problem—the cause of such pain—certain clinico-experimental data have been gathered which are presented here in the hope that they may elucidate or amplify certain phases of the subject.

METHOD OF STUDY

The following observations are based, for the most part, on our own experiments, which were repeated on many occasions to insure accuracy. In some experiments, members of the intern or technical staff of the Hospital were of considerable help to us.

The extremity most frequently used was the arm. It was first elevated to facilitate venous return and to prevent congestion. An ordinary sphygmomanometer cuff, applied just above the bend of the elbow (or the knee), was rapidly inflated to 200 mm. Hg, thereby inhibiting arterial flow. A limb thus deprived of its circulation is capable of performing a sharply limited amount of work before pain sets in. This is unusually severe and aching in character, and rapidly increases until it becomes unbearable and prevents further effort. The standard test which we employed was rhythmic contraction and extension of the fingers at a rate of approximately 40 times per minute. Although the number of contractions that were possible for different subjects varied, the number for the same person in other tests, made under the same conditions, was remarkably constant. In general, our subjects were able to make between 38 and 65 contractions before the pain became unbearable. In but a single instance was one of them able to perform more work—a veritable feat of 100 forceful movements during ischemia. No mention need be made of the effect of rate of contraction or the amount of work done,[1, 3, 5, 6] for these variables were purposely excluded.

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RESULTS

I. Influence of Muscular Exercise Prior to Circulatory Arrest.—1. Local exercise has a profound influence upon the ability to carry out work during ischemia. Forty vigorous flexion and extension movements of the fingers were made, followed by circulatory arrest and then work in the usual manner. The result was clear cut and conclusive: perhaps ⅓ to ½ of the usual number of contractions could be made, i.e., only 16 contractions were possible for a person who had been consistently capable of making 40 such motions. This confirms the results originally obtained by Lewis, et al.[1]

2. Exercise of the whole body also tends to diminish the amount of work that can be carried out subsequently by an ischemic limb. After stationary running movements at a good rate for 5 minutes, fewer contractions were possible (34 for a person who usually made 40 contractions). Because the total amount of work done in running is unquestionably more than that done by an arm alone, some explanation for the quantitative difference between local and general exercise must be made.

II. Nontransferability of Pain From Lower to Upper Extremities.—Cuffs were applied to both legs above the knee. The subject performed work during ischemia by flexing and extending both feet. Sixty contractions were made before pain caused a halt. Both cuffs were then deflated to permit free blood flow for 40 seconds, during which time the blood from the exercised regions entered the general circulation. Thus blood from the legs eventually reached the upper extremities in less than two complete circuits around the body. A cuff was then applied to one of the arms, and work was done in the usual manner. The number of contractions was identical with the normal number, indicating clearly the lack of influence of the preceding exercise.

III. Phase of Recovery.—Restoration of the circulation invariably results in almost instantaneous and complete disappearance of pain.[1] At the same time, the bright pink flush of reactive hyperemia and a feeling of warmth distal to the point of occlusion appear. Paresthesias, such as tingling and "pins and needles" sensation, become quite prominent in the fingers; they persist for a variable period of minutes.

The relationship of the phase of recovery to the amount of work that is possible during ischemia is best illustrated by an experiment of this nature: An ischemic limb, which was capable of performing 40 contractions, had its circulation restored for 15 seconds, followed by rearrest and exercise. Only 11 contractions were possible before the appearance of disabling pain. With restoration of the circulation for one minute, 17 contractions could be made; for two minutes, 22; for three minutes, 34; and, for 5 minutes, 44, which was the maximum number. Inasmuch as the same results occurred regularly in different subjects, we became convinced that, with a minimum of three minutes, and certainly of five minutes, the working muscles recover sufficiently to be able to do the basic amount of work during ischemia. This interval

was therefore taken in subsequent experiments as the time needed for reversal of the fatigue and pain process.

Incomplete restoration of the circulation has a rather curious effect. The pressure in the cuff is reduced by stages of 10 mm. Hg. Almost complete relief of pain is obtained at 150 mm. Hg (it will later be shown that the systemic pressure is elevated by activity during ischemia; in this case, blood inflow occurs at 150 mm. Hg). Within a few seconds, however, the pain reappears in full force and is, by contrast, even more painful and vise-like than before. If the pressure is dropped further, relief is again experienced, only to have the pain return once more. At 120 to 130 mm. Hg, only a feeling of heaviness and fatigue exists. At this point the skin is lividly hyperemic. The pain disappears completely at 80 mm., which is the diastolic level.

IV. Influence of Temperature on the Ischemic Limb.—If the ischemic extremity is heated by immersion in a water bath at a temperature of 115° F., a feeling of fatigue, disinclination to move the part, and, finally, cramplike pain in the wrist and muscles of the forearm develop. The pain in the wrist is especially severe, and occasionally the arm has to be withdrawn, so intense does it become. These sensations begin shortly after exposure to heat and are intense in from five to thirteen minutes; the time variations are dependent, in our estimation, on the insulation of the limb, i.e., a thick arm, with much subcutaneous fat, requires more time for heat to penetrate to the musculature than a thinner extremity. In all probability this is the reason why pain is felt so intensely in a superficial region like the wrist. Removing the arm from the bath decreases the intensity of the pain but does not relieve it completely; this is possible only with restoration of the circulation. The pain in the muscles is similar to that caused by work during ischemia, but is not as severe nor does it reach its peak as rapidly. These sensations are in marked contrast to what happens with simple arrest of the circulation.

Subjecting the arm to a lowered temperature by immersion in water at 60° F. caused no pain or paresthesias even after fifteen minutes of exposure. The only noticeable effects were a feeling of fatigue in the flexor muscles of the forearm and the rather marked cadaveric lividity of the skin.

If the ischemic arm is heated at 110° F. until stiffness and aching occur in the muscles of the forearm, and, at this point, it is called upon to work as in previous experiments, fewer contractions are possible before intolerable pain is reached. In one instance (KH) only 31 contractions could be made; in another (IDS), only 32. Each of these subjects was capable of making 38 to 42 contractions during ischemia, without heating. The reverse holds true with cooling; the number of contractions that are possible before reaching the end point is definitely greater; in other words, the pain process is retarded.

V. Influence of Vasodilatation.—The possibility that ischemic pain might be caused by excessive stretching of the arterioles and finer sub-

divisions of the arterial tree as a result of the vasodilatation which regularly accompanies circulatory arrest in a limb has been suggested.[7] In order to avoid the effects of changing the temperature, which is the usual method of producing active hyperemia, we employed reactive hyperemia (Grant and Pickering) and reflex hyperemia (Landis and Gibbons). Neither of these methods, in contrast to heating directly, increases tissue metabolism.

To produce reactive hyperemia, in an arm in which the circulation had been occluded for 10 minutes, the circulation was restored, and, as the hyperemia reached its maximum (in from a few to twenty seconds), the circulation was rearrested and work begun. Repeated observations showed that the capacity for work remained unchanged; 38 to 40 contractions could still be made when vasodilatation was present.

To bring about reflex hyperemia, both legs were immersed in a water bath at 110° F. while the circulation in one arm was arrested. Within 20 minutes there was a rise in the temperature of the forefinger on the nonoccluded side from 75° F. to 95.5° F. Inasmuch as such a temperature rise is the maximum, vasodilatation in the extremities should have been complete. Yet there was no pain in the occluded limb, and the number of muscle contractions during ischemia was 37, which was nearly normal for this subject. The length of the period of occlusion—twenty minutes—may well have produced a slight diminution of the exercise tolerance.

VI. Influence of Oxygen.—Whether diminution of the oxygen supply to the working tissues is the cause of ischemic pain has been the subject of much controversy. Lewis, et al.,[1] showed that simple circulatory arrest for fifteen to twenty minutes would produce anoxemia without any painful sensation, and that, if work was attempted at this time, there was no reduction in the number of contractions, in spite of the marked oxygen lack. They went even further to substantiate this statement by showing that, if work during ischemia was halted short of the point at which intolerable pain was reached, the circulation could be kept occluded for many more minutes without the development of pain. Obviously, the muscle exercise must have made tremendous inroads on the amount of oxygen available, as did also the following period, during which arrest was maintained without work. Yet there was no pain. Other workers, notably, Kissin,[4] feel that oxygen lack is the main cause of ischemic pain. Kissin showed that, in a group of normal persons, muscle exercise in a reduced oxygen atmosphere without arrest of the circulation hastened the development of pain. To clear up this problem, the authors conducted the following experiments on each other.

A mixture of 10 per cent oxygen and 90 per cent nitrogen was led into the breathing bag of a Gwathmey anesthesia machine. The gas was breathed and rebreathed from this closed system by regular respiratory movements; within two to four minutes the subjects became extremely cyanotic and dyspneic. The final value for oxygen in the mixture must have been exceedingly low, although no quantitative

estimations were made. While in this anoxic state, contractions during ischemia were made in the usual manner. There was absolutely no change in the amount of work that could be done under these extreme conditions. As a matter of fact, the strongest evidence that anoxia was not a factor was the prompt disappearance of pain when the circulation was restored, while the subject was still anoxemic and dyspneic.

VII. Remote and Reflex Secondary Effects of Ischemic Work.—One of our earlier observations on exercise during ischemia was that, with occlusive pressures of 140 to 180 mm. Hg, oscillations of low amplitude could be seen in the mercury column before any signs of pain had appeared. These oscillations meant that there was some flow of blood under the constricting cuff. Normally, the systolic pressures of these subjects ranged from 110 to 130 mm. Hg. After several trials had shown that no oscillations occurred at 200 mm. Hg, this level was chosen as the occluding pressure. These observations led us to study the blood pressure before and after work during ischemia, and striking and interesting changes were found. The following case illustrates this point:

(24C)	Normal B.P.	120/86
	After work during ischemia* (40 contractions)	170/110
	On release of occlusion	130/90
	1½ minutes after release	120/90
	2 minutes after release	120/86

Even exercise of one finger during ischemia, in this case the little finger, caused an appreciable rise in pressure:

(25D)	Normal B.P.	118/80
	After work during ischemia (90 contractions)	136/90

Both the systolic and diastolic pressures are affected. In contrast, simple ischemia results only in a minimal systolic rise (4 to 6 mm. Hg). Restoration of the circulation causes not only prompt disappearance of muscle pain and ache, but also return of the blood pressure to its resting level. Both changes take place with the appearance of reactive hyperemia.

The pulse rate, even when work was done during ischemia, tended to remain unchanged. However, after restoration of the circulation, there was a fall of 5 to 10 beats in some instances. Variations in the size of the pupils were too small to allow us to ascertain whether adrenalin was released by reflex stimulation of the adrenal glands.

VIII. Pain Originating in Nonmuscular Tissues.—In the following group of experiments we attempted to study pain from nonmuscular tissues, and the factors affecting its production. The procedure was the same as that outlined under "Method of Study," except that the finger, rather than the entire limb, was used for testing; the finger was taken to represent a nonmuscular organ.

*Taken on nonoccluded side, of course.

Immersing it into water at a temperature of 115° F. resulted, within one minute, in a stinging and stabbing type of pain which increased rapidly so that, in another thirty to sixty seconds, the sensation became very unpleasant. Some relief was brought about by removing it from the bath. Re-immersing the finger at this time caused the pain to appear even more quickly.

Cooling the ischemic finger in ice water did not result in any painful sensation.

In these respects, the fingers respond like the muscles of the forearm, except for the nature of the pain and the rapidity of its onset.

A finger treated by histamine or mecholyl iontophoresis becomes hyperemic. This finger responds in the usual way to heating and cooling when the arm is made ischemic, that is, pain appears in 1½ to 2 minutes in the one instance, and not in the other. If the finger is treated with adrenalin by the same method of ion transfer, it becomes blanched because the superficial vessels are constricted. When heat is now applied, almost immediately there is severe, stabbing pain which necessitates immediate removal of the finger. Even with the circulation normal, the adrenalin-treated finger, when immersed in hot water, becomes exceedingly painful, although not quite as much so as if circulatory arrest were present. The reaction occurs only if the finger is exposed to heating; otherwise, there is no pain in the blanched finger.

These facts make it clear that the pain of ischemia is not limited to muscular tissue; it may also arise from the ischemic skin (and probably to some extent from subcutaneous tissue). The pain which originates in ischemic skin differs from that arising in the muscle. Whether this difference can be attributed to the type of sensory end organ concerned, and whether the cause of the pain is the same in both instances are questions which cannot be answered with any degree of certainty at this time.

DISCUSSION

A most plausible explanation of ischemic pain has been advanced by Lewis, et al.[1] It lays emphasis on the muscular activity by which the metabolites responsible for the pain are elaborated, and on the circulatory stasis which creates the physical condition that permits these metabolites to accumulate in the cells and tissue interspaces, where they may reach a concentration sufficient to irritate or stimulate the sensory end organs. This substance or group of substances has been designated by Lewis as the *pain factor, or P factor.* Although it has not been isolated or even identified, clinical observations by others, as well as ourselves, lend support to the possibility that it exists. Muscular activity during ischemia, when viewed in this light, means an increase of the P factor to the level of pain production. Mention has been made of the effect of muscular work prior to circulatory arrest. Local exercise (of the upper extremity) greatly curtails the amount of work that is possible during ischemia; general exercise shortens it to a lesser extent. Superficially,

these facts seem inconsistent because the total amount of work done during vigorous exercise is unquestionably greater than during exercise of the arm alone. The difference is readily explained. P factor is produced in each case, but, after local work, even with the circulation normal, some must still be retained in the tissues of the arm. With subsequent contractions during ischemia the threshold level is therefore reached sooner, i.e., with fewer contractions. After vigorous body exercise, however, before blood from the exercised regions reaches the muscles of the forearm, the P factor contained in the arm has been dissipated or destroyed to such an extent that it can be of minor importance only, i.e., produce a diminution of only 6 to 8 contractions. It is the concentration of P factor at the place of activity which determines the onset and intensity of pain, not the P factor produced at some more remote area. This also explains the nontransferability of pain from the lower to the upper extremities.

The influence of temperature changes on the ischemic limb has been presented. Ordinarily, in such an extremity there would be no pain even after twenty to thirty minutes of circulatory arrest. But heating increases the metabolic activities of the tissues, augments the production of metabolites, and causes pain to appear. This may be increased by concomitant muscular exercise, so that the combination of both types of activity allows fewer contractions during ischemia. Just the reverse is true when the limb is cooled, i.e., there is a retardation of the pain process. The similarity between the pain produced by exercise and that produced by heating the forearm has already been discussed. They appear to differ only in the rapidity of onset and in intensity. This has been ascribed to the total increase in tissue metabolism, which is much faster with muscular exercise. Environmental changes may therefore influence the rate of production of the P substance, and, under the proper ischemic conditions, may help it accumulate to the effective pain level.

The effect of temperature has some clinical bearing. In the treatment of peripheral vascular disease it has been stressed time and time again that heating a limb with impaired circulation is not without inherent danger. It is common experience that, after some forms of heat treatment, the patient may complain of increased pain.[8] An adequate explanation for the pain after such treatment is the impetus it gives to the formation of P substance; disease of the vascular tree has produced partial ischemia of the limb. Cooling has been used clinically to diminish tissue metabolism and thus pain sensation. The inconvenience of this mode of treatment and certain undesirable side reactions preclude its general acceptance.

That painful sensation may originate in nonmuscular tissues under certain conditions of circulatory arrest and increase in metabolic activity has been demonstrated. As we pointed out in a previous communication,[9] the simple assumption that pain is caused by accumulation of heat in the ischemic tissues is not tenable. The striking effect

of a topical application of adrenalin militates against this theory. It can only constrict the surface vessels, without altering the physical properties of the finger. One is forced to assume that this sensation represents true ischemic pain in the skin. Its nature is different from that produced by muscular work during ischemia. Instead of being dull, aching, and rather difficult to localize, it is sharp, stinging, and stabbing in nature, and is referred directly to the offending area. The difference may be accounted for by the difference in the character of the sensory end organs in the two regions. Clinically, one meets with the same phenomenon. In intermittent claudication the pain is dull and aching in character, and is referred to the calves or the ankles; with superficial necrosis it is sharp, stinging, burning, or stabbing, and is referred directly to the toe.

Relief from pain is obtained by restoration of the blood flow. Without this, such alternatives as stopping exercise or removing the source of heat cannot suffice for any appreciable period. Partial removal of the obstruction to blood flow has the same effect; the pain is relieved for a short time, only to return with increased intensity until the circulation is completely restored. The minimum time required for reversal of the pain process in the phase of recovery is at least three minutes. During this period, resumption of blood flow washes away or destroys enough P factor in the region of the nerve endings so that the usual amount of work during ischemia may be repeated.

Among the theories as to the cause of ischemic pain have been two opposing ones, namely, excessive vasoconstriction and excessive vasodilatation. The basis for the first theory is probably the analogy between the vasospasm (and pain) induced by cold in Raynaud's syndrome, and the fall in tissue temperature produced by circulatory arrest. Lewis, et al.,[1] showed conclusively, as did Rein and Schneider,[10] that vasodilatation regularly occurs distal to the point of occlusion, and is probably due to the local effect of metabolites (lactic acid, CO_2, histamine, acetylcholine, adenosine-phosphoric acid). This fact and the lack of effect of reactive hyperemia and reflex hyperemia certainly cast great doubt on the validity of both theories. Even more conclusive was the effect of injecting vasodilating substances into the arterial tree. Although intense hyperemia resulted, it was unaccompanied by any semblance of pain. These observations will be presented in a later paper.

The much disputed role of oxygen in relation to the development of ischemic pain was touched upon. Lewis held that the oxygen content of the blood is not primarily responsible for the pain; later work by Kissin[4] tended to disprove this, and his statement carries some weight to the present day. The extreme anoxic states reached in the course of these experiments and the lack of influence on the tolerance to activity during ischemia would seem to confirm the original view of Lewis.

Finally, a word must be said about the changes in blood pressure and pulse rate which occur with exercise during ischemia. A fairly

marked rise in both systolic and diastolic levels is observed long before the pain threshold is reached, so that it cannot be the result of the pain. The pulse and respiratory rates are only slightly increased. Reid[6] noticed the same phenomena in his studies on the effects of simple ischemia. He thought that the precipitate fall in blood pressure to the usual level, or even below, when the blood flow was restored was caused by "the sudden release of the products of metabolism . . . . and the sudden cessation of afferent impulses with removal of pain . . . ." Alam and Smirk[11] felt that the blood pressure rise was caused by passage of nerve impulses from the exercised muscle to the vasomotor center. The stimulus which started the reflex and maintained it during circulatory arrest was the accumulation of muscle metabolites. Since this view fits into the muscle metabolite theory of ischemic pain, we are inclined to favor it; the P factor may indeed be responsible for both mediation and causation of a blood pressure rise, as well as pain. It is possible that a reflex release of adrenalin from the adrenal glands may be the direct cause of the blood pressure elevation. This offers an attractive field for further study.

SUMMARY AND CONCLUSIONS

In a limb whose circulation has been arrested, an increase in tissue activity, whether caused by muscular activity or heating of the tissues, results in painful sensations. Even nonmuscular tissues may be affected in the same process. The relationship of the pain to the so-called P substance has been outlined. Other factors, which appear to exert little or no direct influence, are vasodilatation, vasoconstriction, and the amount of oxygen supply to the tissues.

REFERENCES

1. Lewis, T., Pickering, G. W., and Rothschild, P.: Observations Upon Muscular Pain in Intermittent Claudication, Heart **15**: 359, 1931.
2. Lewis, T.: Pain in Muscular Ischemia; Its Relation to Anginal Pain, Arch. Int. Med. **49**: 713, 1932.
3. Katz, L. N., Lindner, E., and Landt, H.: On Nature of Substance(s) Producing Pain in Contracting Skeletal Muscle, etc., J. Clin. Investigation **14**: 807, 1935.
4. Kissin, M.: The Production of Pain in Exercising Skeletal Muscle During Induced Anoxemia, J. Clin. Investigation **13**: 37, 1934.
5. Reid, C.: Behavior of Limb Muscles and Nerves During Experimental Ischemia, Quart. J. Exper. Physiol. **19**: 127, 1929.
6. Reid, C.: Experimental Ischemia: Sensory Phenomena, Fibrillary Twitchings and Effects on Pulse, Respiration and Blood Pressure, Quart. J. Exper. Physiol. **21**: 243, 1931.
7. Leiner, Georg: Zur Behandlung der arteriellen Embolie, Klin. Wchnschr. **16**: 639, 1937.
   Also, from personal communication from Dr. Leiner.
8. Wright, I. S.: Physical Therapy in Peripheral Vascular Disease, Arch. Phys. Therapy **19**: 161, 1938.
9. Harpuder, K., and Stein, I. D.: Studies on the Cause of Pain in Ischemia, Arch. Phys. Therapy **23**: 218, 1942.
10. Rein, H., and Schneider, M.: Die Auswirkung künstlicher Mangeldurchblutung auf den lokalen Stoffwechsel, Arch. f. d. ges. Physiol. **239**: 451, 1937.
11. Alam, M., and Smirk, F. H.: Observations in Man Upon a Blood Pressure Raising Reflex Arising From the Voluntary Muscles, J. Physiol. **89**: 372, 1937.

STUDIES ON THE NATURE OF PAIN ARISING FROM AN ISCHEMIC LIMB

II. Biochemical Studies

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THE substance (or substances) responsible for ischemic pain has been designated the *pain factor, or P factor,* by Lewis. Some of its properties and the factors which influence its development are already known.[1, 2] Most important for the purpose of this study, namely, its identification, was the knowledge gained from clinical observations.[3] It must be capable of production or mobilization within the one and one-half to two minutes which elapse between occlusion of the circulation and the completion of work during ischemia. It must also be capable of destruction or dispersion by the blood stream in the few seconds which follow restoration of the circulation. Finally, it must revert to its original level in the tissues (and the blood) within the three to five minutes of the recovery phase, after which the muscles can again perform the usual amount of work during ischemia.

METHODS OF STUDY

The only practical method of obtaining information about tissue metabolism in the intact human being is an indirect one, namely, examination of the blood stream for the substances brought to the tissues by the arteries, and the substances elaborated there and removed by the veins. Because the ischemic state obviously precludes transport of substances by way of the arteries, our studies were confined to the venous blood. In another part of this study, several of the suspected substances were introduced intravascularly in an effort to reproduce the pain of ischemia.

Samples of blood were taken from an antecubital vein, without stasis. The first, or *rest,* sample was withdrawn from the control arm with its normal blood circulation. Then the blood flow in the other arm was rapidly cut off by applying a pressure cuff above the bend of the elbow and maintaining a pressure of 200 mm. Hg. Rhythmic extension and flexion of the fingers were performed at a rate of approximately 40 per minute. As soon as intense pain appeared (after 40 to 60 contractions), the needle was inserted into a deep antecubital vein and the cuff quickly deflated. There was a 5- to 10-second wait before the next, or *exercise,* specimen was withdrawn, so that the sample would contain blood from the deeper tissues. The entire time required for collection was usually less than a half minute. A third sample was taken exactly three minutes after restoration of the circulation in the exercised arm. This corresponded to the minimum period required for *recovery,*[3] and the specimen was so labelled.

Preliminary steps were begun without delay. Before doing plasma or serum analyses, the samples were recentrifuged to remove all traces of cellular elements.

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I. CHEMICAL STUDIES ON BLOOD

Lactic Acid.—First among the substances to be investigated with respect to the cause of pain was lactic acid. In addition to the fact that it is an important metabolite of muscular activity, its ability to shift the acid-base balance to the acid side had made it a ready target in the search for the hypothetical pain factor. Moore and Moore[4] made this inference in their work on the pain sensibility of arteries, although there was no attempt to confirm the possibility by actual test. Katz, et al.,[2] likewise suspected that lactic acid was the substance responsible for ischemic pain.

When blood samples were taken in the manner described and analyzed by the gasometric method of Avery and Hastings,[5] the results showed clearly that lactic acid could not possibly be the pain factor, in the light of the criteria already outlined.

Representative analyses are shown in Table I.

TABLE I

LACTIC ACID (MG. PER CENT)

CASE	REST	WORK DURING ISCHEMIA	RECOVERY
20C	12.3	29.0	40.7
21C	10.4	28.2	34.2
22A	10.4	28.0	32.6

The increase in lactic acid during the period of recovery, when all trace of pain had disappeared, discredits any claim that it is responsible for the pain. Indeed, we have observed it to increase, as have others,[6] and to remain elevated for some time after resumption of blood flow, as more of it is "washed out" from the deeper tissues. As for its effect on shifting the acid-base balance, simultaneous estimation of the CO_2 combining power of the blood serum showed that it remained unchanged with this amount of exercise during ischemia. The "outpouring" of lactic acid must be effectively neutralized. Katz, et al.,[2] reported that ischemic pain is hastened by acidity and retarded by alkalinity. Their results, however, were obtained by procedures which required inhalation of 10 per cent CO_2 and the ingestion of large amounts of sodium bicarbonate. Such conditions are extreme, and do not pertain to the more physiologic limitations of work. Maison and Forster,[7] in studying the pH of intercellular fluid during ischemic muscle contraction by means of a capillary glass electrode inserted into the belly of the working muscle, showed that there was an increase in acidity which reached its maximum many minutes after the circulation had been restored and pain had disappeared. The moderate changes which they observed in the pH of intercellular muscle fluid seem to parallel closely the curve of formation of lactic acid during exercise. Such a degree of acidity obviously does not change the alkali reserve of the blood, as shown by our experiments. At any rate, their results

agree with our contention that neither lactic acid nor a shift in acid-base balance has anything to do with the problem of ischemic pain.

Histamine.—Attention was centered on this substance because Anrep and Barsoum[8] had claimed that it was liberated during muscle contraction and was responsible for the hyperemia which ensued. Reasoning further along this line, it was conceivable that histamine might be the substance involved in the theory which regards excessive stretching of the vessel walls during vasodilatation[9] as the cause of ischemic pain. Furthermore, it has already been implicated by Rosenthal and Minard[10] as the cause of pain in the denuded or injured skin.

Blood samples were collected from our normal subjects in the usual manner; the amount of histamine was estimated by Code's modification[11] of Barsoum and Gaddum's method, using guinea pig's ileum for assay. Inasmuch as our estimations showed that histamine in whole blood remained unchanged during the course of the experiments, it was thought possible that the expected increase[8] might be so small that it would be detected earlier in the plasma. Such a search, however, likewise proved fruitless (Table II).

TABLE II

HISTAMINE

CASE	SPECIMEN	REST	WORK DURING ISCHEMIA	RECOVERY
29A	whole blood	0.05 gamma/c.c.	0.04	0.04
30C	whole blood	0.14	0.10	0.10
34A	plasma	–	none*	–
34C	plasma	none*	none*	none*
35A	plasma	none*	none*	none*

*Only minimal, nonspecific contractions obtained.

Inasmuch as the values of histamine were well within the normal range, there is no proof that histamine itself is the pain substance or that the vasodilatation it might produce (in conjunction with other metabolites) results in the painful sensations that arise in ischemic tissues. The discrepancy between our figures and those of Anrep and Barsoum is undoubtedly to be explained by the difference in the nature of the two investigations. They employed dogs, and subjected them to much more muscular work than our subjects accomplished. A recent study by Kwiatkowski[12] substantiates our results; he, too, was unable to find an increase in histamine in either human whole blood or plasma, even after reactive hyperemia.

Many other substances were sought and found wanting, according to our criteria for a possible role in the pain process.

Blood Ammonia.—Embden, et al.,[13] had shown that ammonia was released from adenosine-phosphoric acid during muscular exercise under pathologic conditions, and possibly also under physiologic ones. It was conceivable that this might be the pain substance, especially since Maison[14] had shown how painful the injection of ammonium salts was.

Analyses were made by the Conway micromethod,[15] and there was no difference in the three samples.

Blood Adrenalin.—According to Bacq,[16] intermediary oxidation products of adrenalin (adrenoxine) have vasodilating and inhibiting actions. McDowall and McWham[17] and others have also shown that adrenalin itself may behave as a vasodilator in muscle. For that reason adrenalin and its oxidation product were estimated by the Shaw modification[18] of the Whitehorn method. Although this method is not entirely satisfactory, the complete absence of any change in adrenalin content was sufficient proof that neither it nor its oxidation products are involved in ischemic pain.

Oxidation Potential.—This was studied because of the possibility that, in the absence of oxygen, incompletely oxidized metabolites which would change the oxidation potential of the tissues and eventually of the blood might be formed. Such changes might be parallel, and indicative of the cause of ischemic pain. The methods employed were both colorimetric (brilliant cresyl blue, methylene blue chloride, sodium 2, 6-dichlorbenzenoneindophenol) and potentiometric (Beckman potentiometer, using a blank platinum electrode). Again no appreciable differences could be found in the three samples of blood serum.

Conductivity of Sera.—This might serve as an indicator of the possible alteration of the total electrolyte balance in the blood serum coincident with the appearance and disappearance of ischemic pain. There was no essential change in the three samples, as shown by the Beckman potentiometer.

Serum Potassium.—Potassium was of particular interest in this connection because of its high concentration in muscle cells. It influences many of the fundamental properties of muscular tissues, notably those of irritability and contractility, and participates in a multiplicity of seemingly diverse, remote effects during the intermediary action of adrenalin and acetylcholine. Furthermore, Moore, Moore, and Singleton[19] found that the potassium ion was extremely irritating when injected into the femoral arteries of narcotized cats, and suggested "that accumulation of acid metabolites or potassium ion in inflamed areas is more important to production of pain than increased tissue-tension." The quantitative method employed by us was that of Weichselbaum, Somogyi, and Rusk.[20] This proved to be both convenient and accurate. Even small amounts could be estimated, and duplicate and triplicate checks differed by less than one milligram per cent. In other words, the small variations of potassium ion concentration in our experiments were significant. The three standard samples were withdrawn from each one of our subjects and analyzed. As has been stated, all erythrocytes were removed by double centrifuging to obviate any error caused by this factor (Table III).

Potassium proved to be the one substance which was regularly increased by ischemic work, but fell quite promptly to its original level

TABLE III

SERUM POTASSIUM IN VENOUS BLOOD OF NORMAL PERSONS

CASE	CIRC. NORMAL BEFORE EXERCISE	CIRC. OCCLUDED AFTER EXERCISE	CIRC. NORMAL RECOVERY	REMARKS	
1	16.5	20.2	15.1	49 contractions	
2	14.4	16.8	14.8	50 contractions	
3	13.5	18.9	14.6	45 contractions	
4	16.7	22.6	16.0	47 contractions	
5	21.0	22.7	19.6	39 contractions	
6	19.0	22.9	17.6	50 contractions	
7	21.8	24.8	19.0	35 contractions	
8	20.0	23.6	19.4	46 contractions	
9	19.7	22.1	18.4	42 contractions	
10	16.7	18.9	15.3	50 contractions	
11	17.0	18.7	17.0	35 contractions	
12	—*	18.7	16.5	50 contractions	*1st spec. lost.
13	14.6	17.2	13.4	55 contractions	
14	19.6	24.9	19.3	100 contractions	
15	16.9	19.0	16.9	54 contractions	
16	19.6	25.0	19.3	38 contractions	
17	21.1	23.0	20.9	54 contractions	
18	16.5	19.4	16.2	64 contractions	
19	18.2	21.2	17.8	65 contractions	
20	22.1	24.2	21.7	55 contractions	
21	19.2	21.5	18.3	65 contractions	
22	17.4	20.0	17.0	55 contractions	
23	15.3	18.2	14.8	65 contractions	
	Average increase		3.0 mg./100 c.c. potassium		
	Minimum increase		1.6 mg./100 c.c. potassium		
	Maximum increase		5.9 mg./100 c.c. potassium		

within three minutes after restoration of the circulation. The smallness of the rise in serum potassium in relation to the profound events initiated by it needs no more comment than a statement that its increase in the blood does not necessarily mirror the content of the tissue cells and intercellular fluid, inasmuch as animal experimentation by Noonan, et al.,[21] has shown a temporary lack of equilibrium between the potassium in these locations and the blood proper.

Contrasted with this increase in the potassium ion during ischemic work is the fact that it remains normal after almost double the same amount of work when the latter is done with an intact circulation.

TABLE IV

CASE	REST (CIRC. NORMAL)	WORK (CIRC. NORMAL)
39B–GR	15.4	15.7
39C–KH	16.9	17.4
39D–MS	21.6	21.2

Superficially, these results seem to belie the studies of Fenn and Cobb,[22] which show an increase in potassium after muscular contraction and stimulation. One must not forget, however, that these figures were obtained on animals, and that the period of stimulation lasted as long as a half-hour or more before a significant increase was obtained. Our

experiments on human beings were closer to being physiologic. We were unable to demonstrate a rise in potassium during exercise with a normal circulation, although we do not doubt such an increase exists. It must, however, be fleeting. The situation is modified by slowing or halting blood flow, for, in this way, potassium accumulates instead of being promptly washed away.

In order to exclude any influence of circulatory arrest alone on the potassium level, in several experiments we occluded the circulation to one arm for 2½ minutes. This was perhaps a minute longer than the usual period of exercise during ischemia. Nevertheless, there was no effect on the potassium level.

TABLE V

CASE	CONTROL CIRC. NORMAL	AFTER 2-3 MINUTES CIRC. OCCLUDED
40A–KH	17.0	17.2
40B–IDS	19.2	18.7
40C–MG	20.0	19.2

To obviate any possibility that blood concentration in the ischemic region might possibly alter the potassium level, hematocrit readings were made (Table VI). They showed that hemoconcentration did not occur.

TABLE VI

CASE	REST, WITH CIRC. NORMAL		AFTER ISCHEMIC WORK	
	R.B.C. (%)	PLASMA (%)	R.B.C. (%)	PLASMA (%)
55A Tr	47	53	47	53
55B Bo	44	56	45	55
55C St	51	49	52	48

Heating the ischemic forearm has been shown to cause a characteristic aching pain like that produced by exercise during ischemia, but not as intense or as rapid in onset. These differences[3] we attributed to the varying amounts of time required for the muscles to be heated through the insulating barrier of skin and subcutaneous tissue, and the marked difference in the effect on tissue metabolism of the two methods; exercise undoubtedly has a much greater effect. The effect of heating on the potassium level in the ischemic arm, although not constant and not too impressive, is interesting, and favors the contention that it might be increased tissue metabolism rather than any definite metabolic phase of muscle contraction which liberates the potassium ion.

II. INTRAVASCULAR INJECTIONS

A great many substances have been introduced into the human body in attempts to influence the development of pain, e.g., the ingestion of acid or basic substances to change the pH (Katz, et al.[2]), the percutaneous injection or application of histamine (Rosenthal and Minard[10]), the subcutaneous and intramuscular injections of various ions by

TABLE VII

CASE	REST CIRC. NORMAL	OCCLUSION AND HEATING AT 115° F.	RECOVERY 3 MIN. AFTER RELEASE	REMARKS
49B KH	19.2 mg. % K	22.0 mg. % K	18.8 mg. % K	Increase in K
49C GR	17.1 mg. % K	20.2 mg. % K	16.7 mg. % K	Increase in K
50A IW	19.4 mg. % K	19.4 mg. % K	20.7 mg. % K	No increase with heating
50B AS*	18.7 mg. % K	18.9 mg. % K	18.7 mg. % K	No increase with heating
51A KH	17.8 mg. % K	20.7 mg. % K	17.8 mg. % K	Increase in K

*Only mild pain experienced after 15 minutes' immersion in water bath at 115°. This subject was able to make 100 ischemic contractions of his arm before severe pain was experienced. Possibly insufficient heating explains the result in this case.

Maison,[14] and the intravascular introduction of extremely irritating solutions[23] which were so painful that frequently general anesthesia had to be employed to lessen the effect.

Our objections to most of this work have been two: (1) the quantities introduced far exceeded physiologic limits, and (2) the route of injec-

TABLE VIII

	CASE	SUBSTANCE	VESSEL	RESULT
(A) VASODILATING SUBSTANCES	35B	Papaverine ½ gr.	A. Fem.	Hyperemia of limb
	36D	Papaverine ½ gr.	A. Fem.	Hyperemia of limb
	36G	Mecholyl 100 gamma	A. Fem.	Hyperemia, gooseflesh, sweating of limb
	35C	Histamine 50 gamma	A. Fem.	Hyperemia of limb
	35D	Histamine 50 gamma	V. Fem.	Flushing of face
	36C	Histamine 60 gamma	A. Fem.	Hyperemia of limb
	36B	Histamine 75 gamma	A. Fem.	Hyperemia of limb
(B) POTASSIUM CHLORIDE (1% SOLUTION)	41A	KCl 5-10 mg.	A. Fem.	No ardent reaction (insuff. amt.)
	41B	KCl 20 mg.	A. Fem.	No ardent reaction (insuff. amt.)
	48B	KCl 10 mg.	A. Brach.	No ardent reaction (insuff. amt.)
	49A	KCl 20 mg.	A. Brach.	No ardent reaction (insuff. amt.)
	48A	KCl 30 mg.	A. Brach.	Agonizing pain persisting for 20 min. and disappearing gradually.
	52C	KCl 30 mg.	A. Brach.	Very severe pain and slight vasodilatation. Effects persisted for ¾ hr.
	54A	KCl 30 mg.	A. Brach.	Very severe pain and slight vasodilatation which persisted for 15 min.
	54B	KCl 30 mg.	A. Brach.	Very severe pain persisting for 10-15 minutes and accompanied by slight vasodilatation
	56A	KCl 70 mg.	Antecub. V.	Control—no effect
	56B	KCl 100 mg.	Antecub. V.	Control—no effect

tion and the irritating nature of the solutions themselves precluded any possibility that the conclusions drawn could be reliable.

Although the injection of suspected substances intra-arterially in the attempt to reproduce the pain of muscular ischemia is, at best, a crude physiologic method, it was nevertheless done with varying amounts of vasodilating substances and an isotonic solution of potassium chloride (Table VIII).

Substances such as histamine, papaverine, and mecholyl, with their known dilating effect on vessels in muscular tissue, do not produce pain upon intra-arterial injection, which is the most reliable and direct method of placing these metabolites in the vicinity of the muscle cells.

Potassium, on the other hand, when introduced in sufficient amount, produces such severe pain that it could be tried on but few subjects. The pain started a few seconds after injection and spread distally to the hand and fingers in the next 20 to 30 seconds. Our subjects, after they recovered sufficiently to be able to talk, called it the most severe pain they had ever experienced, and described it as "aching," "like a cramp," "sharp and hard," etc. The pain rapidly reached its acme and continued to be most severe for ten to twenty minutes. A mild, but definite, hyperemia of the skin was present throughout this period. The muscle power was markedly impaired; the subjects volunteered the information that the arm was "weak and they couldn't move it well." After the intense pain had diminished, muscle soreness distal to the point of injection in the forearm invariably occurred. This lasted as long as ¾ hour or more.

DISCUSSION

The potassium ion, which is preponderantly intracellular, plays an important role in tissue metabolism. Muscle cells are especially rich in potassium. Baetjer[24] showed that, if the blood flow to the hind limb of the cat was reduced by mechanical occlusion or by vasoconstriction from sympathetic stimulation, the amount of potassium in samples from the femoral vein was suddenly augmented by 60 per cent or more when the rate of blood flow had been reduced to 20 per cent of its normal value. This was thought to be caused by liberation of potassium from the muscle fibers as a result of asphyxia, not by concentration of blood or diffusion of potassium from the erythrocytes into the plasma. Since then, independent investigations have shown that any asphyxial state, not only local vascular occlusion, may produce the same increase in potassium. It must be emphasized again that these studies were carried out on animals, and under conditions far removed from those of our experiments. The time factor, mode of occlusion, and other conditions were not analogous to those of our experiments on human beings. For example, we found no increase in potassium after circulatory arrest of two to three minutes. We do not mean to imply that this might not

occur in more extreme conditions comparable to those in the animal experiments.

Fenn and his co-workers have clearly demonstrated that in electrically stimulated muscles of various experimental animals there is a loss of potassium in exchange for sodium and a gain of water. A further contribution was the evidence that, after voluntary contraction, the same diminution of potassium in muscle and a corresponding increase in the amount liberated to the blood plasma occurred; the loss of potassium was proportional to the amount of work done. This increase of potassium started simultaneously with the onset of muscle stimulation and contraction, and the amount returned to normal in the blood stream within five minutes after the stimulation had ceased.

Other bits of experimental evidence seem to fit into this composite picture which we have been presenting. Katz and Katz,[25] as well as Feldberg and Guimarais,[25] have pointed out that the intra-arterial injection of potassium results in the liberation of adrenalin from the adrenal glands. Dawes[26] has further shown that potassium chloride not only causes vasodilatation in probable muscle, but also a general rise in blood pressure due to the release of adrenalin.

Potassium enters into all of these intricate and closely bound relationships—asphyxial states, blood pressure rise, vasodilatation, secretion of adrenalin, etc. It is the only constituent of the tissues which fits our criteria for the P substance; it is a normal tissue metabolite found in great concentration in the muscle cells. It is released from the muscle during exercise and in anoxemic states. During ischemic exercise of one to one and one-half minutes' duration it is liberated simultaneously with the development of pain, and accumulates sufficiently to appear in increased concentration in the blood stream. It is capable of rapid dispersion as soon as the circulation is restored, and returns to its normal level within three to five minutes thereafter. Finally, potassium is the one substance which, when injected intra-arterially in isotonic solution and in amounts which might ordinarily be released physiologically from a corresponding mass of contracting muscle,[27] produces such severe pain that we could try it on but a few subjects. This pain is, in many respects, like the severe aching sensation complained of after ischemic work, but intensified and magnified. It is not due to irritation of the arterial wall because there is a latent period of several seconds before pain begins, implying penetration to more distal regions, and because the amount required depends on the mass of tissue affected. Thus, the amounts which produced severe pain in the arm had absolutely no effect on the leg. The intravenous injection of double or triple the amounts used for intra-arterial injection was absolutely innocuous and produced no symptoms. The difference must be explained by dilution, in the latter instance, by the blood before it reaches the end organs in the muscles; in the former it is transferred by the most physiologic and direct route to the muscle cells.

One cannot say from this evidence that potassium *is* the P factor itself, but only that it is intimately bound up with the phenomena of pain in the ischemic state in some way that is not yet clear. Although our own injection experiments seem to show a direct effect of the potassium ion on the nerve endings in the tissues, one cannot exclude the possibility that some reflex or even physicochemical change initiated by the release of potassium might be a factor. It may well be asked why there is no apparent effect on pain production in diseases such as periodic familial paralysis and Addison's disease, in which profound alterations in potassium levels, even greater than those we have found, are known to occur. In explanation of this, we wish to stress once more that the level in the blood does not necessarily mirror the changes taking place in the tissues, and that, in so far as pain sensation is concerned, it may be the sudden change in potassium concentration around the sensory receptors during ischemic contraction which is involved.

SUMMARY

It is suggested that potassium plays a major role in the genesis of ischemic pain; this hypothesis is based partly on experimental work on animals, and, to some extent, on the clinical observations and biochemical studies we have presented.

During muscular activity potassium is liberated from the cells. Under ischemic conditions, a physical factor is introduced which leads to a rapid accumulation of the potassium ion until it reaches the threshold required for stimulating the pain end organs in the muscle.

It is further assumed that an increase in the activity of tissues other than muscle, possibly skin, might also result in discharge of potassium, and, under suitable ischemic conditions, result in pain.

REFERENCES

1. Lewis, T., Pickering, G. W., and Rothschild, P.: Observations Upon Muscular Pain in Intermittent Claudication, Heart **15:** 359, 1931.
2. Katz, L. N., Lindner, E., and Landt, H.: On Nature of Substance(s) Producing Pain in Contracting Skeletal Muscle, etc., J. Clin. Investigation **14:** 807, 1935.
3. Harpuder, K., and Stein, I. D.: Studies on the Nature of Pain Arising From an Ischemic Limb. I., Am. Heart J. **25:** 429, 1943.
4. Moore, R. M., and Moore, R. E.: Studies on the Pain-Sensibility of Arteries. I., Am. J. Physiol. **104:** 259, 1933.
5. VanSlyke, D., and Peters, J. F.: Quantitative Clinical Chemistry, Baltimore, 1932, Williams & Wilkins Co., Vol. II, p. 427.
6. Lang, E. P.: Observations on Lactic Acid, Total CO_2 and pH of Venous Blood During Recovery From Severe Exercise, Am. J. Physiol. **107:** 687, 1934.
7. Maison, G. L., and Forster, A. C.: pH Changes in Ischemic Human Muscle After Voluntary Contraction, Am. J. Physiol. **125:** 735, 1939.
8. Anrep, G. V., and Barsoum, G. S.: Appearance of Histamine in Venous Blood During Muscular Contraction, J. Physiol. **85:** 409, 1935.
9. Leiner, G.: Zur Behandlung der arteriellen Embolie, Klin. Wchnschr. **16:** 639, 1937.
10. Rosenthal, S. R., and Minard, D.: Experiments on Histamine as the Chemical Mediation for Cutaneous Pain, J. Exper. Med. **70:** 415, 1939.
11. Code, C. F.: The Quantitative Estimation of Histamine in the Blood, J. Physiol. **89:** 257, 1937.

12. Kwiatkowski, H.: Observations on the Reaction of Histamine to Reactive Hyperemia, J. Physiol. **100:** 147, 1941.
13. Embden, G., Carstensen, M., and Schumacher, H.: Spaltung und Wiederaufbau der ammoniakbildenden Substanz bei der Muskeltätigkeit, Ztschr. f. physiol. Chem. **179:** 186, 1928.
Parnas, J. K., Lewinski, W., Jaworska, J., and Umschweif, B.: Ueber den Ammoniakgehalt und die Ammoniakbildung im Froschmuskel, Biochem. Ztschr. **228:** 366, 1930.
14. Maison, G. L.: Studies on the Genesis of Ischemic Pain: The Influence of the Potassium, Lactate and Ammonium Ion, Am. J. Physiol. **12:** 315, 1939.
15. Conway, E. J., and Byrne, A.: The Microdetermination of Ammonia, Biochem. J. **27:** 419, 1933.
16. Bacq, Z. M.: "Adrenoxine"; Its Production From Adrenalin and Its Action. Proceedings of the Physiological Society, Feb. 12, 1938, J. Physiol. **92:** 28, 1938.
17. McDowall, R. J. S., and McWham, I.: Adrenalin Dilatation. Proceedings of Physiol. Society, J. Physiol. **88:** 11, 1937.
18. Shaw, F. H.: The Estimation of Adrenalin, Biochem. J. **32:** 19, 1938.
19. Moore, R. M., Moore, R. E., and Singleton, A. O., Jr.: Experiments on the Chemical Stimulation of Pain-Endings Associated With Small Blood Vessels, Am. J. Physiol. **107:** 594, 1934.
20. Weichselbaum, T. E., Somogyi, M., and Rusk, H. A.: A Method for the Detection of Small Amounts of Potassium, J. Biol. Chem. **132:** 343, 1940.
21. Noonan, T. R., Fenn, W. O., and Haege, L.: The Distribution of Injected Radioactive Potassium in Rats, Am. J. Physiol. **132:** 474, 1941.
22. Fenn, W. O., and Cobb, D. M.: Electrolyte Changes in Muscle During Activity, Am. J. Physiol. **115:** 345, 1936.
Fenn, W. O.: Loss of Potassium in Voluntary Contraction, Am. J. Physiol. **120:** 675, 1937.
23. Brooks, B.: Intra-Arterial Injection of Sodium Iodide, J. A. M. A. **82:** 1016, 1924.
Singleton, A. O.: Use of Intra-Arterial Injections of Sodium Iodide in Determining the Condition of the Circulation in the Extremities, Arch. Surg. **12:** 1232, 1928.
24. Baetjer, A. M.: The Diffusion of Potassium From Resting Skeletal Muscles Following Reduction in the Blood Supply, Am. J. Physiol. **112:** 139, 1935.
25. Katz, G., and Katz, G.: Action of Potassium Chloride, and Calcium Chloride on the Adrenals of the Cat, J. Pharmacol. & Exper. Therap. **59:** 284, 1937.
Feldberg, W., and Guimarais, J.: Liberation of Acetylcholine by Potassium, J. Physiol. **86:** 306, 1936.
26. Dawes, G. S.: The Vasodilator Action of Potassium, J. Physiol. **99:** 224, 1941.
27. Fenn, W. O.: The Distribution of Excess Potassium in Cats. "Livro de Homenagem" to Professors Alvaro e Miguel Osorio de Almeida, Brazil, 1937.

THE RELATIONSHIP OF CONGENITAL HEART DISEASE TO PREMATURE BIRTH

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IN ORDER to elucidate the possibility of a direct or mutual relationship between prematurity of birth and congenital cardiovascular defects, or of a common dependence on some abnormality of germ plasm or fetal life, we have carried out a twofold study. First, in order to learn whether prematurity is a factor that may favor the development of congenital heart disease, we have examined, with the kind permission of the staff, the autopsy protocols of prematurely born babies at the Boston Lying-In Hospital, and have ascertained the incidence of such maldevelopment. Second, we have found out how often prematurity of birth occurred among patients with congenital heart disease who attended the Out-Patient Departments of the Massachusetts General Hospital, Children's Hospital, and Boston Lying-In Hospital. We have ascertained, in almost all these cases, the birth weight, and have assembled a special group of patients who weighed less than 2,500 grams (5.5 pounds) at birth, in accordance with the criteria proposed by Ylppö.[1] This author made a common group of all babies who weigh less than 2,500 grams because they are incompletely developed, in poor condition for an independent life, and have some characteristic stigmata. Most of the babies of this group are born prematurely, but they may be born at full term or even past term. Thus, Capper[2] found that, in fifty-six of 437 cases in which the infants weighed less than 2,500 grams, the duration of the pregnancy was not known; 276, or over 72 per cent, were born prematurely, 103, or 27 per cent, were born at full term, and two were past term (these two weighed 1,800 and 2,300 grams, respectively, at birth). That is why some American authors designate as "immature infants" those that weigh less than 2,500 grams, and call "premature infants" those who are born before term, that is, before the 270th day of the pregnancy. At the Boston Lying-In Hospital it has been the custom to call infants that weigh less than 5 pounds (2,268 grams) premature, and below 5½ pounds (2,495 grams), immature. The criterion of the weight not only has clinical significance, but is useful also because, as we have observed many times, it is impossible to know the exact duration of the pregnancy, and because statistics about prematurity are based largely upon the birth weight. Body length would probably be the best criterion of all, but it is not routinely recorded and is often difficult to measure in the first place.

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A. AUTOPSIES ON PREMATURELY BORN BABIES

The records of 139 autopsies on prematurely born babies were examined; the birth weight of 129 of them was less than 2,500 grams. The duration of life after birth had been, in most instances, only a few hours; the longest period of life was eight days. Of all the 129 infants who weighed less than 2,500 grams at birth, the weight of the heart was more than 17 Gm. in only eleven; this is the average normal heart weight of a full term baby. The weights of the sixteen hearts in the whole group of 139 that weighed more than 17 grams were 30, 27, 27, 22, 20, 20, 20, 19, 19, 19, 19, 19, 18, 18, 18, and 18 grams, respectively. In no case was closure of either the foramen ovale or the ductus arteriosus recorded.

There were only three cases of malformation of the heart among the 139 premature infants (2.2 per cent); these were as follows:

CASE 1.—Interventricular septal defect, 7 mm. in diameter, behind the left lateral leaflet of the tricuspid valve. The weight of the heart was 20 grams.

CASE 2.—Multiple congenital malformations of the lungs, heart, and intestine. The right auriculoventricular valve had only two cusps. The pulmonary veins emptied into the superior vena cava, at approximately 7 mm. from the opening of this vessel into the right atrium. The fossa ovalis measured 1 cm. in diameter, and was only partly closed by a veil-like septum which left patent approximately half of the foramen. The pulmonary artery was normal. At a point 4 mm. from the free edge of the posterior cusp of the pulmonary valve, a small opening, measuring no more than 1 mm. in diameter, was found. This opening continued into a small artery which passed upward and entered the left lung, where it divided into several smaller branches which supplied both left and right lungs. Immediately above this opening the ductus arteriosus began; it was 1.1 cm. in circumference and 1.2 cm. long. The left atrium was of approximately normal size, but no blood vessels coming from the lungs were found entering it. Immediately below the foramen ovale, in the left atrium, there was a small opening which measured about 1 mm. A probe inserted into this opening passed between the trabeculae of the right atrium.

CASE 3.—Anomaly of the vessels of the aortic arch: the right and left common carotid arteries arose together to form a short common trunk as the first branch of the aortic arch. The second branch was the left subclavian. The third was the right subclavian, which left the aortic arch posteriorly and passed behind the trachea to reach the right side.

The infant whose heart weighed 30 grams had, in addition, hepatomegaly, renomegaly, and splenomegaly.

If we consider the 129 infants who weighed less than 2,500 grams, the incidence of congenital malformation of the heart was three cases, or 2.3 per cent. Including all the 139 cases, the incidence was still only three cases, or 2.1 per cent.

B. PATIENTS WITH CONGENITAL HEART DISEASE

We have examined the histories of a large group of patients with congenital heart disease, and looked for the birth weight and evidence

of prematurity, and have sent letters asking for this information in the cases in which it was not recorded. We have obtained such data on 188 patients. These we have divided into two groups:

1. Patients whose birth weight was known. There were 148 of these. Seventeen of them, or 11.4 per cent, weighed less than 2,500 grams.

2. Patients concerning whom it was specified whether or not birth was premature. There were 172 of these, of whom seventeen, or 9.8 per cent, were born prematurely.

In the whole group of 188 patients there were twenty-one with patency of the ductus arteriosus, all of whom were born at full term. In nineteen of the twenty-one the birth weight was recorded as being less than 2,500 grams in only one case, that is, 5.2 per cent. Patency of the ductus is, of course, actually a postnatal development, although its potentiality may rightly be considered congenital. There were four patients with an interauricular septal defect, all of whom were also born at full term. Among the thirteen cases of the tetralogy of Fallot seen at the Children's Hospital, there were only two premature births.

DISCUSSION

A priori, we may suppose that there are two critical periods in the development of the heart with regard to congenital malformation: the first between the fifth and eighth weeks, at which time the involution of the bulbus and the formation of the septa take place, and the second after birth, when the ductus arteriosus and the foramen ovale close.

Patten[3] has demonstrated that the foramen ovale is normally open at birth, when it is possible to pass a probe through it, although functionally it should be considered closed. He considers three periods in the closure of the foramen ovale. The first covers the first month after birth, during which a probe can be passed freely. The second period lasts six to eight months, when the foramen ovale is reduced to a slit and the movable valve is converted into a fixed septal structure; passage of a probe is still possible, but more difficult. Finally, during the last period the valve of the foramen ovale adheres to, and becomes a part of, the interauricular septum. Patten considers incomplete adhesion of the valve, with patency to a probe, as a variation of the normal, because it is found in 25 per cent of normal adult hearts.

Christie[4] studied 590 normal hearts of children who were between one day and one year old, and found that closure of the foramen ovale occurred before the twelfth week after birth in 87 per cent of the cases. Closure of the ductus arteriosus took place before the eighth week after birth in 88 per cent of these cases.

Ylppö[1] studied the closure of the ductus arteriosus in immature children, and found that, in most of them, one or two weeks after birth, the ductus arteriosus was no longer permeable by the blood coming from the aorta.

Some authors have supposed that prematurity of birth would tend to favor persistence of the ductus arteriosus or of the foramen ovale. Hess, Mohr, and Bartelme[5] found, in 385 autopsies on premature infants, twelve cases of definite cardiac malformations, that is, 3.1 per cent (including five cases of ventricular septal defect, the commonest of the anomalies). This percentage is about the same as that which we found in autopsies on premature babies.

Dioxades[6] thinks that prematurity should favor the persistence of certain characteristics of the fetal heart, namely, the relatively small left ventricle and relatively big left auricle, the relatively big right ventricle and relatively small right auricle, and persistence of the foramen ovale.

In Capper's series[2] of 437 premature infants who were followed to the age of 14.5 years, there were ten patients, or 2.3 per cent, with congenital heart disease, seven of which were autopsied; the other three were alive, and the type of their lesions was not specified. The postmortem diagnoses in the seven autopsy cases were: simple foramen ovale in one, foramen ovale and patent ductus arteriosus in three, aneurysm of the ductus arteriosus in one, pulmonary stenosis in one, and dextrocardia with pulmonary stenosis in one.

As we have said, the incidence of prematurely born children in our series of cases of congenital heart disease was 11.4 per cent, considering only those who weighed less than 2,500 grams. What is the general incidence of premature and immature births? It varies a great deal with statistics. Ylppö[1] states that the figure is 5 per cent in Moscow (there were 6,036 children with a birth weight of less than 2,500 grams out of 121,626 deliveries). Pinard, Hahn, and François (cited by Ylppö[1]) found 29,071 "premature" infants (babies with a birth weight of less than 2,500 grams) out of 188,204 births in France, which is 15.4 per cent. Ylppö[1] calculates that in Germany the incidence of immaturity is over 10 per cent. Schultze[7] found 6.6 per cent immaturity among 10,355 new-born children. American statistics give lower figures. Einhorn[8] found 204 immatures that weighed less than 2,500 grams among 12,335 infants born in Albany, that is, 3.47 per cent. Wilcox[9] found 330 children that weighed less than 2,500 grams among 10,163, that is, 3.24 per cent. Hess[10] reported an incidence of 3.77 per cent among 49,425 infants. At the Boston Lying-In Hospital, information based on 27,713 births from 1933 through 1940 shows an incidence of premature births (1- to 5-pound infants) which varies annually from 2.9 to 3.5 per cent, and, of immature infants (below 5½ pounds), that varies from 4.5 to 5.5 per cent. Since our analysis should be compared with these various American figures, it does appear that at least twice as many of our patients with congenital heart disease were premature as in a control series of the population at large.

SUMMARY AND CONCLUSIONS

1. Among 139 autopsies on prematurely born children we found only three cases (2.2 per cent) of congenital malformation of the heart.

2. Among 148 patients with congenital heart disease whose birth weight was known, we found seventeen who weighed less than 2,500 grams at birth, that is, 11.4 per cent. Among 172 cases in which the duration of pregnancy was ascertained, there were seventeen patients who were born prematurely, that is, 9.8 per cent.

3. The incidence of prematurity of birth in our cases of congenital heart disease was about twice that in deliveries of infants with normal hearts. Nevertheless, it happened that only one of nineteen patients with patency of the ductus arteriosus (in reality a postnatal development) of this series weighed less than 2,500 grams at birth, all four patients with auricular septal defects were born at full term, and only two of thirteen patients with the tetralogy of Fallot were premature.

REFERENCES

1. Ylppö, A.: Zur Physiologie, Klinik, und zum Schicksal der Frühgeborenen, Ztsch. f. Kinderk. **24**: 1, 1919-1920.
   Ylppö, A.: Pathologisch-anatomische Studien bei Frühgeborenen, Ztsch. f. Kinderk. **20**: 212, 1919.
2. Capper, A.: The Fate and Development of the Immature and of the Premature Child, Am. J. Dis. Child. **35**: 443, 1928.
3. Patten, B. M.: The Closure of the Foramen Ovale, Am. J. Anat. **48**: 18, 1931.
   Patten, B. M.: Developmental Defects of Foramen Ovale, Am. J. Path. **14**: 135, 1938.
4. Christie, A.: Normal Closing Time of the Foramen Ovale and the Ductus Arteriosus (An Anatomical and Statistical Study). Am. J. Dis. Child. **40**: 323, 1930.
5. Hess, J. H., Mohr, G. J., and Bartelme, P. F.: The Physical and Mental Growth of Prematurely Born Children, Chicago, 1934, University of Chicago Press.
6. Dioxades, L.: Fetalismus des Kardiovasculärensystem, Ztschr. f. klin. Med. **108**: 321, 1928.
7. Schultze, K. W.: Das Schicksal von 683 Frühgeburten, Ztschr. f. Geburtsh. u. Gynäk. **118**: 405, 1939.
8. Einhorn, M. B.: The Premature Infant: A Statistical Study, New York State J. Med. **402**: 1380, 1940.
9. Wilcox, D. A.: A Study of Three Hundred and Thirty Premature Infants, Am. J. Dis. Child. **52**: 848, 1936.
10. Hess, J. H.: The Chicago City-Wide Plan for the Care of Premature Infants, J. A. M. A. **107**: 400, 1936.
    Benner, M. C.: Premature Closure of Foramen Ovale, Am. Heart J. **17**: 437, 1939.
    Brown, J. W.: Congenital Heart Disease, London, 1939, John Bale Medical Publications, Ltd.
    Dunham, E. C., and McAlenney, P. F.: A Study of 244 Prematurely Born Infants, J. Pediat. **9**: 717, 1936.
    Gross, P.: The Patency of the So-Called "Anatomically Opened but Functionally Closed" Foramen Ovale, Am. Heart J. **10**: 101, 1934.
    Guassardo, G.: Studi sul cuore degli immaturo, ricerche electrocardiografiche, teleradiografiche e rilievi anatomodimensionale, Riv. di clin. pediat. **38**: 321, 1940.
    Mall, F. P.: On the Development of the Human Heart, Am. J. Anat. **13**: 249, 1912.
    Waddell, W. W., Purcell, C. W., and Wray, W. S.: Premature Infants. A Clinical Study of 432 Infants Born Prematurely, South. M. J. **30**: 535, 1937.

HISTOLOGIC DEMONSTRATION OF ACCESSORY MUSCULAR CONNECTIONS BETWEEN AURICLE AND VENTRICLE IN A CASE OF SHORT P-R INTERVAL AND PROLONGED QRS COMPLEX

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THERE has been much speculation concerning the mechanism responsible for the electrocardiographic anomaly of an abnormally short P-R interval in association with a prolonged QRS complex. That it may occur in presumably undamaged hearts is strongly suggested not only by the pioneer study of Wolff, Parkinson, and White,[1] but by subsequent reports, as well. Recently, Hunter, Papp, and Parkinson[2] have listed the various hypotheses which reflect the efforts made to account for the phenomenon.

The hypothesis of an accessory pathway of A-V conduction was first suggested as a possible explanation by Holzman and Scherf,[3] in 1932. The same hypothesis was advanced independently by two of us, and subjected to analysis in the light of what was then known about the subject, in a paper[4] which was in press at the time Holzman and Scherf's article appeared. It has continued to seem to us to be the only explanation thus far proposed for this phenomenon[5] which offers no violence either to mathematical probability or to generally accepted views regarding the spread of the excitatory process. Moreover, the recently reported ingenious experiments of Butterworth and Poindexter[6] show that similar electrocardiograms, with a short P-R interval and prolonged QRS complex, can be produced in animals by the introduction of an artificial, accessory pathway.

So far as we are aware, no one has yet presented histologic proof of the existence of accessory muscular connections between the auricles and ventricles of a patient with this type of electrocardiographic abnormality. The present paper furnishes this proof.

CASE REPORT

A. F., a 13-year-old boy, was admitted to the Allentown State Hospital for the Insane on April 30, 1935. He was under the care of Dr. A. Lindenfeld, to whom we are indebted for much of this information. Examination on admission showed no evidence of cardiovascular disease; the heart was not enlarged; the rate was 74 per minute; there were no auscultatory abnormalities; and no history suggesting heart disease or reduced exercise tolerance was obtained. His diagnosis was "Behavior problem with borderline intelligence."

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On October 18, 1936, while playing football, he had his first known attack of paroxysmal tachycardia. The cardiac rate was 180 per minute and the rhythm was regular. He was cold, clammy, and dyspneic, and had pain in the right upper quadrant of the abdomen. He was given an injection of morphine. After about an hour, he coughed up a small amount of bloody sputum, and the attack terminated. The next day premature beats were noted. One of us (G. D. G.) saw him after this attack and could elicit no evidence of cardiovascular disease. Thereafter his heart was studied repeatedly by physical examination and by special methods. A teleroentgenogram showed that it was normal in size and shape; the transverse diameter was 12.5 cm., with a chest diameter of 27 cm. The electrocardiogram showed a short P-R interval, a prolonged QRS complex, and abnormal T waves (Fig. 1). Since he was powerfully built and athletic in type, with no demonstrable abnormality except that in his electrocardiogram, his activities were not restricted. In December, 1937, he was said to be playing basketball, without cardiac symptoms.

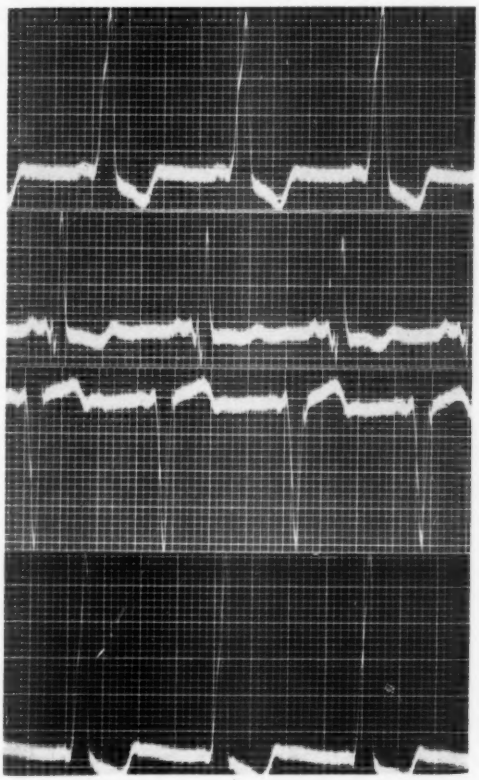

Fig. 1.—Electrocardiogram of A. F., taken May 12, 1938, showing the short P-R interval and prolonged QRS complex.

On March 27, 1938, a routine physical examination showed nothing new. On March 31, 1938, after riding on a merry-go-round, he experienced dizziness, palpitation, severe substernal distress, and shock. He was in a cold sweat, and seemed very ill. The heart rate was "over 150." He was helped back to the dormitory. Carotid sinus pressure was ineffective. After seven hours, the paroxysm of tachycardia ceased spontaneously.

On April 28, 1938, one of us (G. D. G.) examined him again. A somewhat accentuated second sound was heard at the base of the heart. Exercise was followed

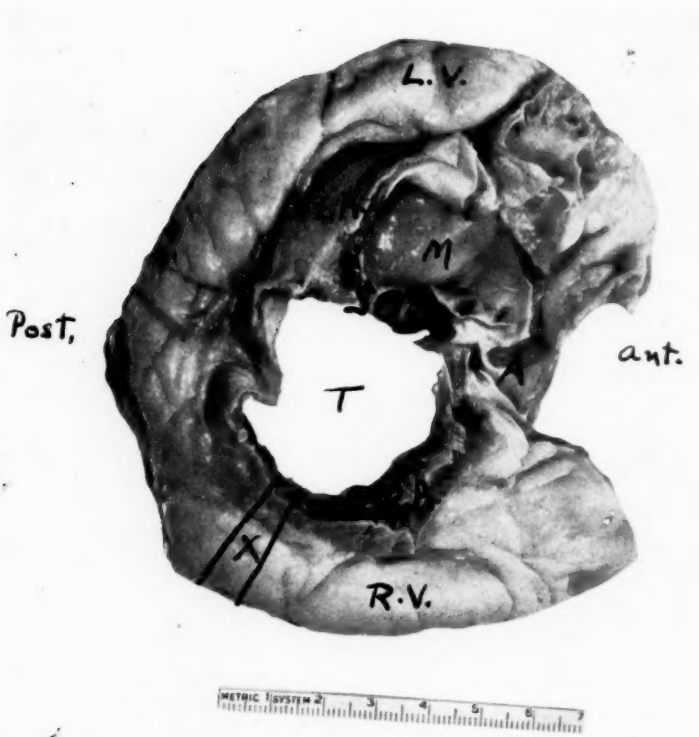

Fig. 2.—A portion of the heart of A. F. to show the manner in which it was prepared for serial section, and to indicate the location of the accessory muscular connections between auricle and ventricle, which are shown in Figs. 3 and 4. The ventricular tissue 2 cm. below, and the auricular tissue 1 cm. above, the auriculoventricular groove were cut away. The remaining part of the heart was placed on a flat surface, with the ventricles against that surface, and photographed from above. Thus one is looking down on the auricular part of the preparation, with the anterior part of the heart to the right; the right auricle (*RA*) and the right ventricle (*RV*) are below; the posterior part of the heart is to the left; the left auricle (*LA*) and left ventricle (*LV*) are above. *S* is the septum, *A* is the aorta, *M* is the mitral valve, and *T* is the tricuspid orifice. *X* indicates the region in which the muscular connections between the right auricle and right ventricle, shown in Figs. 3 and 4, were found.

Fig. 3.—Photomicrographs of sections taken through the auriculoventricular groove at position *X* (Fig. 2), showing the first muscular connection that was found between the right auricle and ventricle. All sections were stained with Masson stain, which colors the muscle red and the connective tissue green. Photographed in black and white, using a green filter, the contrast is fairly definite, but not so sharp as in actual sections. It is much more convincing to follow these muscular connections by looking at each successive slide. However, this figure is an attempt to demonstrate in a few key photographs the appearance of the first muscular connection which we encountered. In the photographs the muscle is dark and the connective tissue light. Magnification 37×. (*a*). (Section 1164A) The auricular muscle (*A*) is shown to the right, the ventricular muscle (*V*) to the left, and the ventricular cavity (*VC*) below, with a "bay" above a projection (*P*). Beginning near the right upper corner of the picture, a bridge of muscle (*B*) is seen extending down and to the left, and curving back toward the right again, just beneath the endocardium. Just to the left of this structure, across the bay and jutting into the ventricular cavity, is a portion of the ventricular muscle (*M*) which in subsequent sections will be seen to unite with the muscle in the bridge (*B*) and then rejoin the main ventricular muscle. (*b*). (Section 1171A) The auricular muscle (*A*) is shown above and to the right, the ventricular muscle (*V*) below and to the left, and the ventricular cavity (*VC*) below, with a "bay" above the projection (*P*). Across the upper part of this "bay" the bridge of muscle (*B*) is beginning to pass. This muscle tissue now is separated from the auricular muscle by fibrous tissue, and is projecting out into the "bay." Continuous with the ventricular muscle (*M*) which, in section 1164A, was jutting out into the "bay," is the island (*M*), now lying free in the "bay," just to the left of *B*. (*c*). (Section 1172A) The general relationships of auricular muscle, ventricular muscle, and ventricular cavity are much like those in section 1171A. The bridge of muscle (*B*) has projected much further out into the bay, and has almost become an "island," just to the right of the island (*M*) described in Fig. 3*b*. (*d*). (Section 1180A) The bridge of muscle (*B*) now lies free as an "island" in the "bay" just to the right of the island (*M*). (*e*). (Section 1189A) The bridge of muscle (*B*) has united with the island (*M*) and is continuous with the ventricular muscle, but the muscle of the two

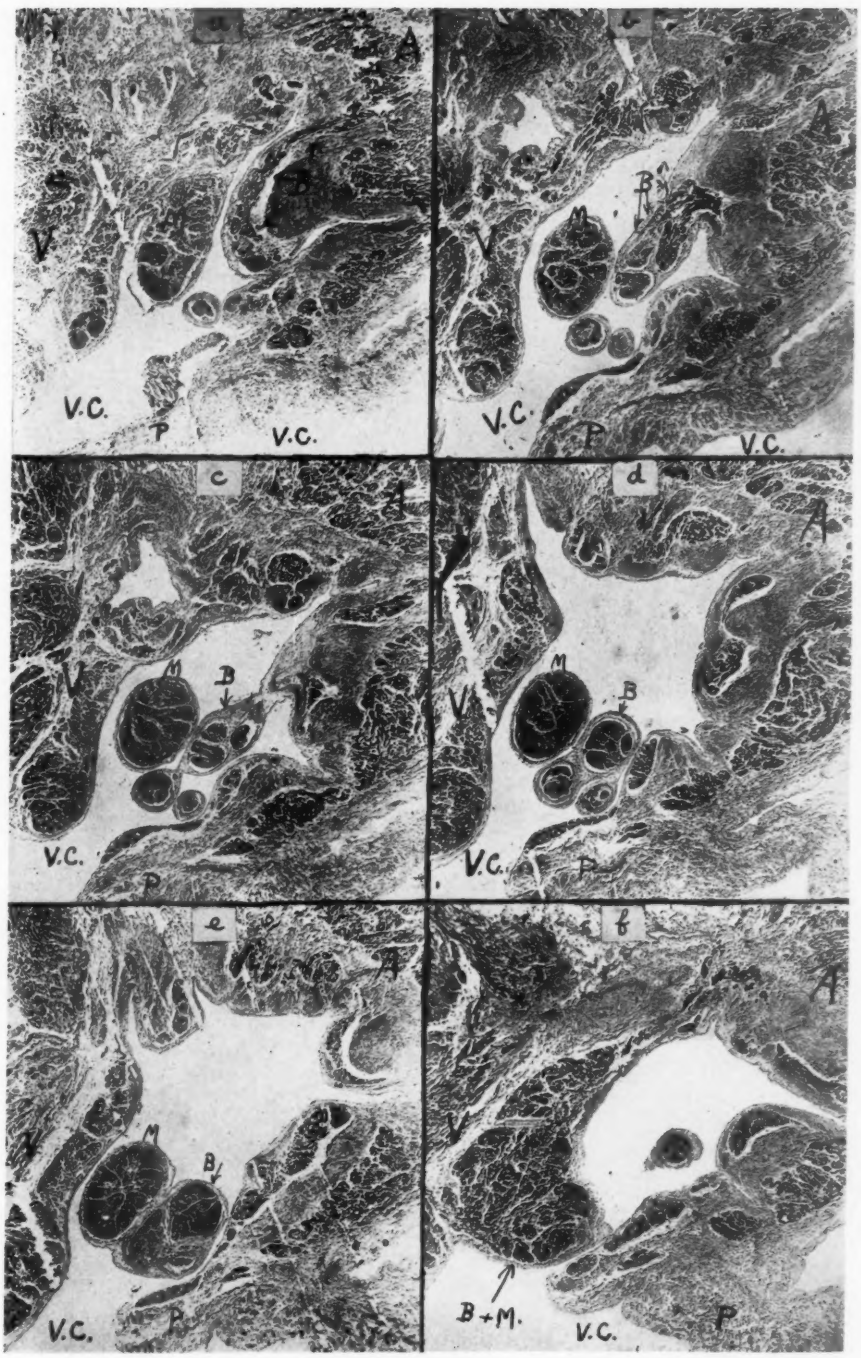

Fig. 3.

structures is still separated by fibrous tissue. (*f*). (Section 1207A) Fibrous tissue no longer separates the components of the "island," derived from auricle and ventricle, as it did in Section 1189A. Moreover, the island *B* + *M* is now seen uniting with the ventricular muscle. Subsequent sections (not shown in this figure) demonstrated that this muscular mass communicated freely with the main mass of ventricular muscle.

Thus this first series of figures shows the first muscular connection which was found. It connects the auricular to the ventricular muscle by forming a bridge over a "bay" in the ventricular cavity. There is no "nodal tissue" in this muscle bridge, such as was described by Kent.

by premature beats. Otherwise, no abnormalities were found on physical examination. On May 12, 1938, electrocardiograms were taken after exercise and after atropine sulfate administration (gr. 1/100 by hypodermic). No definite changes resulted from these procedures. The P-R interval and QRS complexes continued to show the anomaly.

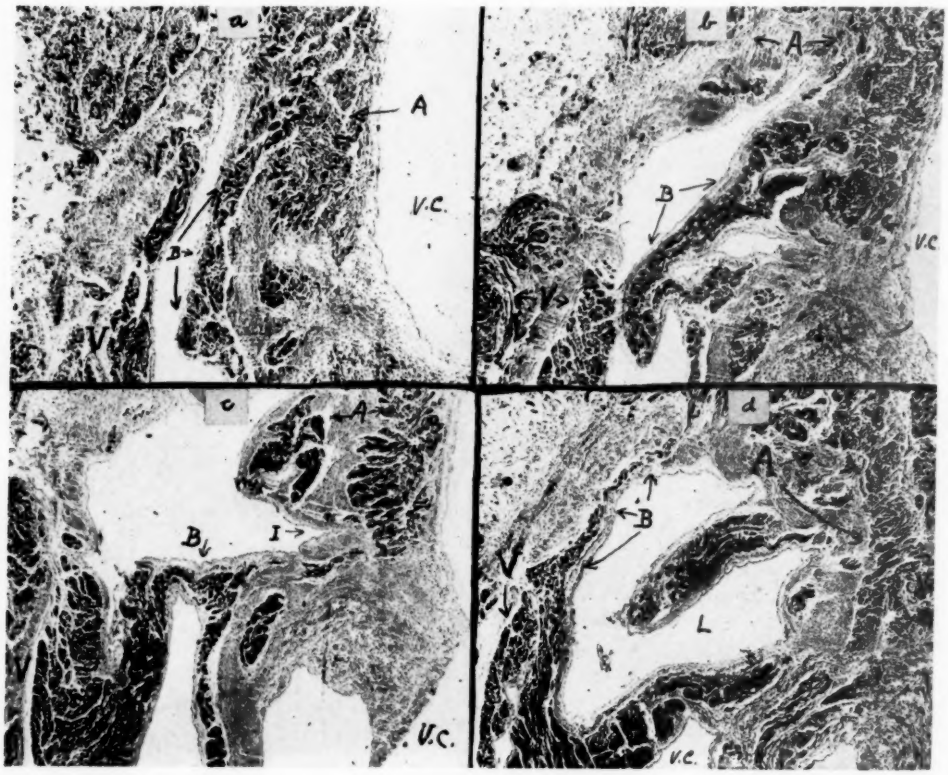

Fig. 4.—A series of four photomicrographs showing the second muscular connection in *a*, *b*, and *c*, and the third muscular connection in *d*. The stain and photography were the same as described for Fig. 3. (*a*). (Section 1230B) The auricular origin of the second muscular connection (*B*) is shown. The ventricular cavity (*VC*) lies to the right. In the middle of the picture is a long narrow "bay" which is part of the ventricular cavity, and which connects with it below and to the right, beyond the limits of this picture. The auricular muscle (*A*) lies above. Extending down from it, along the right side of the "bay," is the beginning of the second muscular connection (*B*). The ventricular muscle (*V*) lies along the left shore of the "bay." (*b*). (Section 1249C) The second muscular connection (*B*) projects across the "bay" and begins to join the "shore" on the left side of the "bay," where the ventricular muscle is situated. As in the preceding section the auricular muscle (*A*) is above and to the right, and the ventricular muscle (*V*) below and to the left. The bay, which is being traversed by the muscular bridge (*B*), is a part of the ventricular cavity. (*c*). (Section 1255B) The second muscular bridge (*B*) passes across the "bay" and joins the ventricular muscle (*V*) which lies along the left side of the "bay." The bridge (*B*) now shows no muscular connection with the auricular muscle (*A*), which lies above and to the right; it is separated by the indentation (*I*) of the "shore of the bay." (*d*). (Section 1269B) The third muscular connection. The auricular muscle (*A*) lies at the top and along the right margin of the picture. The ventricular muscle (*V*) lies below and to the left. A large "lake" (*L*) lies in the center. The third muscular connection (*B*) is the tenuous strand of muscle extending along to the left shore of the "lake." This is the most delicate of the three muscular bridges. It is the only one which may be seen in its entirety in one section, and it is the only one which does not cross the ventricular cavity.

The remains of the second muscular connection which made a "lake" of the upper portion of the "bay" (of Fig. 4*b* and *c*) is seen along the lower margin of the "lake," in Fig. 4*d*, lying in the strip of tissue separating the ventricular cavity (*VC*) from the "lake."

On May 17, 1938, while wrestling with one of his friends (not really fighting), he was seized with palpitation and severe substernal distress. The heart rate was "over 150." An hour later he said he felt better. Two hours after the onset he died suddenly after drinking a glass of water.

Examination of the heart after death disclosed no gross evidence of disease. The organ was not enlarged. The valves and coronary vessels were normal. Nothing was found elsewhere in the body to account for the sudden death.

Histologic Studies.—It was decided to make serial sections around the auriculoventricular groove in an attempt to discover whether or not any evidence could be obtained concerning the hypothesis of an accessory pathway of auriculoventricular conduction,[3-5] i.e., whether there was a muscular connection between auricles and ventricles in addition to the main auriculoventricular bundle. In order to do this, the ventricles were cut off 2 cm. below the auriculoventricular groove, and the auricles were cut off 1 cm. above the groove, as shown in Fig. 2. Blocks of tissue were cut sagittally, beginning just to the right of the aorta. The sectioning was carried around toward the right from that point. Every fifth section was stained and studied.

In section 1161 a muscle bundle was seen leaving the auricular muscle. It joined the ventricular muscle in section 1207, after passing by means of a bridge of tissue across the ventricular cavity just below the attachment of the tricuspid valve. Consequently, every section, instead of every fifth section, was stained from 1158 to 1306, so that there were sections A, B, C, D, and E for each of these numbers. Thus a total of 2897 stained sections was studied.

Figs. 3 and 4 represent an attempt to show the accessory bridges of muscle tissue which were found between the right auricle and right ventricle. Three such connections were found in the general position of the letter X in Fig. 2, at approximately the right lateral border of the heart. Although it might have been interesting to carry the sections completely around the auriculoventricular groove, it was decided to stop when these definite muscular connections were discovered because it seemed that the information desired had already been obtained; namely, that, in the heart of a patient who had had a short P-R interval and an aberrant QRS complex, there were definite muscular connections between auricle and ventricle, bridging the auriculoventricular groove, of a type which should be able to conduct an impulse from auricle to ventricle.

DISCUSSION

At the end of the last century, A. F. Stanley Kent[7] became interested in the problem of the conduction of impulses from auricle to ventricle. He made extensive microscopic studies of the auriculoventricular groove, and published his first observations in 1893,[7a, 7b] describing the auriculoventricular muscular connections which he found in various mammals at different stages of development. He demonstrated by his studies on animals[7a] that young rats and rabbits have a very rich muscular anastomosis between auricle and ventricle. As the age of the animal increases, or as the animal scale is ascended, these muscular connections become fewer in number. The monkey exhibits the fewest auriculoventricular muscular connections, but does have them. (Kent was the first to describe the auriculoventricular bundle, although His' name has been applied to it.)

After these early publications, there was an interval of twenty years before Kent's next papers appeared. In these[7c-7i] his main interest

shifted from the lower animals to man, and he dealt primarily with an auriculoventricular connection which lay at the right border of the heart and connected the right auricle and right ventricle; he called it the "right lateral bundle." He showed a number of photomicrographs of this structure.[7c, 7e, 7g, 7i] It is a very definite muscular bridge between auricle and ventricle. Usually the auricular muscle enters a mass of "nodal tissue" in the auriculoventricular groove, "interposed in the course of the muscular path between auricle and ventricle." However, one of his early photomicrographs fails to show "nodal tissue."[7e] The implication of Kent's statements is that this right lateral bundle was found in all of the human hearts which he studied. However, he did not actually make this statement. He mentioned several experiments performed by himself[7f] and others[7h] which demonstrated to his satisfaction that, in animals, this structure was capable of conducting impulses from auricle to ventricle after the main bundle had been cut. He also referred to observations[7h] which made him feel that the right lateral bundle may function in man in certain cases. However, despite Kent's convincing photomicrographs, interest in the "right lateral bundle" waned, possibly as a result of Lewis' opinion,[8] until the electrocardiographic anomaly which is the subject of this paper began to be investigated.[3, 4]

Recently, Glomset and Glomset[9] stated that there are "definite muscular bridges between auricles and ventricles in various places in the auriculoventricular groove," but they showed no photomicrographs and did not mention the "right lateral bundle" specifically.

The auriculoventricular connections which we are now describing had the following characteristics: (1) Three of them were located at the right lateral border of the heart. Since our study has not been extended further, it is not possible to say whether or not more such connections existed. (2) Two of the three took a rather unexpected course, in that they passed across the ventricular cavity in an actual muscular bridge. (3) No "nodal tissue" was interposed in their course, as described by Kent. Thus, these structures may not be the same as those which Kent described, although they are situated in the same general region.

These observations show that a patient with a short P-R interval and a prolonged QRS complex did have definite muscular connections between auricle and ventricle at the right lateral border of the heart. These connections were of such a nature that they should have been able to conduct an impulse from auricle to ventricle, or from ventricle to auricle.

In our first paper on this subject[4] we attempted to account for abnormalities of the cardiac mechanism, such as paroxysmal auricular tachycardia and fibrillation, in cases of short P-R interval and prolonged QRS complex, by assuming that they are initiated by retrograde conduc-

tion, through the accessory tract, of an excitatory process which had previously been transmitted to the ventricles via the normal channels. The reports of Arana and Cossio,[10] Hunter, Papp, and Parkinson,[2] and Levine and Beeson[11] indicate that there is at least some tendency toward the occurrence of paroxysmal ventricular tachycardia, as well. This could also be accounted for by a somewhat similar assumption, for, if a ventricular extrasystole forced retrograde conduction through the main auriculoventricular tract, and was followed by an aberrant auricular response, as sometimes occurs in cases in which the mechanism is otherwise normal, it might be possible, so far as the time relationships are concerned, for the impulse to be reconducted to the ventricle via an accessory conduction tract if one happened to be present. Thus premature re-entry into ventricular tissue might initiate an abnormality of the ventricular mechanism, just as premature re-entry into auricular tissue might initiate an abnormality of the auricular mechanism. These hypothetical considerations require the assumption of only one accessory pathway between auricle and ventricle. We had not previously entertained the thought that there might be more than one such pathway. The presence of multiple pathways should, it seems to us, facilitate re-entry of the excitatory process.

Thus, this study gives support to the hypothesis of an accessory pathway of auriculoventricular conduction[3, 4] in these cases. Proof of the hypothesis, however, would require direct evidence that tracts such as we have demonstrated are capable of transmitting the excitatory process.

The patient described in this paper differed from the majority with this anomaly, in that he died in an attack of paroxysmal tachycardia, but this is the only difference. The electrocardiogram was typical, attacks of paroxysmal tachycardia are characteristic, and the patient showed no other evidence of cardiovascular disease.

If, as Kent implies, this right lateral bundle exists in all human hearts, the question suggests itself, why do not all of us have a short P-R interval and a prolonged QRS complex? We have no data upon which an answer to this question could be based.

SUMMARY

1. A patient with a short P-R interval and a prolonged QRS complex, and no other evidence of cardiovascular disease, died in an attack of paroxysmal tachycardia.

2. Gross examination of the heart showed no evidence of disease.

3. Serial histologic sections of a portion of the auriculoventricular groove showed three muscular connections at the right lateral border of the heart between the right auricle and right ventricle. Two of these bridged a small part of the ventricular cavity during their course.

4. The demonstration of the presence of these structures, which should be capable of conducting an impulse from auricle to ventricle, furnishes

further support for the hypothesis of an accessory pathway of auriculoventricular conduction as an explanation for this electrocardiographic anomaly.

REFERENCES

1. Wolff, L., Parkinson, J., and White, P. D.: Bundle Branch Block With Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, AM. HEART J. 5: 685, 1930.
2. Hunter, A., Papp, C., and Parkinson, J.: The Syndrome of Short P-R Interval, Apparent Bundle Branch Block, and Associated Paroxysmal Tachycardia, Brit. Heart J. 2: 107, 1940.
3. Holzman, M., and Scherf, D.: Ueber Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, Ztschr. f. klin. Med. 121: 404, 1932.
4. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients With Presumably Undamaged Hearts: Hypothesis of an Accessory Pathway of Auriculo-Ventricular Conduction (Bundle of Kent), AM. HEART J. 8: 297, 1933.
5. Wolferth, C. C., and Wood, F. C.: Further Observations on the Mechanism of the Production of a Short P-R Interval in Association With Prolongation of the QRS Complex, AM. HEART J. 22: 450, 1941.
6. Butterworth, J. S., and Poindexter, C. A.: Short P-R Interval Associated With a Prolonged QRS Complex: A Clinical and Experimental Study, Arch. Int. Med. 69: 437, 1942.
7. Kent, A. F. S.: (a) Proceedings of Physiol. Soc. Nov. 12, 1892, J. Physiol. 14: XXIII, 1893.
(b) Researches on the Structure and Function of the Mammalian Heart, J. Physiol. 14: 233, 1893.
(c) Observations on the Auriculo-Ventricular Junction of the Mammalian Heart, Quart. J. Exper. Physiol. 7: 193, 1913-1914.
(d) The Structure of the Cardiac Tissues at the Auriculo-Ventricular Junction, J. Physiol. 47: 17, 1913-14.
(e) The Right Lateral Auriculo-Ventricular Junction of the Heart, J. Physiol. 48: 22, 1914.
(f) A Conducting Path Between the Right Auricle and the External Wall of the Right Ventricle in the Heart of a Mammal, J. Physiol. 48: 57, 1914.
(g) Illustrations of the Right Lateral Auriculo-Ventricular Junction in the Heart, J. Physiol. 48: 63, 1914.
(h) Neuromuscular Structures in the Heart, Proc. Roy. Soc., London, s.B. 87: 198, 1913-1914.
8. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, 1925, Shaw and Sons, Ltd., p. 13.
9. Glomset, D. G., and Glomset, A. T. A.: A Morphologic Study of the Cardiac Conduction System in Ungulates, Dog, and Man, AM. HEART J. 20: 389, 1940.
10. Arana, R., and Cossio, P.: Fibrilacion auricular y taquicardia ventricular como eventualidad posible en el P-R corto con QRS ancho y mellado, Rev. argent. de cardiol. 5: 43, 1938.
11. Levine, S. A., and Beeson, P. B.: The Wolff-Parkinson-White Syndrome, With Paroxysms of Ventricular Tachycardia, AM. HEART J. 22: 401, 1941.

ACQUIRED PALMAR ERYTHEMA AND CUTANEOUS VASCULAR "SPIDERS"

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DURING the past several years, in a study of the cutaneous arterial "spiders"† which may occur in certain persons with liver disease, pregnancy, and nutritional deficiency disorders, and in apparently normal persons, observations have been made on two hundred fifty-one subjects.[1] These have been followed for periods varying from a few days to five years. Among the associated vascular phenomena, a curious hyperemia of the skin of the palms and sometimes of the soles has been encountered in a few instances.‡ This appears to have an important relation to vascular spiders. A review of the reports of similar cases has been undertaken, and personal observations on eleven new ones will be presented.

In surveying the literature one encounters great difficulty in deciding whether to include certain obscure conditions of the palms and soles among the cases here considered. Reports during the last quarter of the nineteenth century were often vague about details, so that it is difficult to make a diagnosis from the descriptions. Into the category of doubt must fall the erythrokeratosis or erythema keratodes of the soles and palms,[2] and related disorders.[3]

Erythema palmare as a distinct entity was first described in an all too brief note by Chalmers,[4] in 1899, although this paper has not been noticed by subsequent writers. He was impressed by a remarkable palmar redness, symmetrically disposed, and most pronounced in the palmar pads of the hypothenar and thenar eminences. He found the condition only in Europeans who were residing on the Gold Coast of West Africa. There were no symptoms, and the condition was entirely innocuous, although it was apparently widely prevalent in the special group which he studied. No suggestions were put forward concerning the nature of this stigma.

In 1914, there was an interesting discussion of a case presented at a meeting of the British Dermatological Association under the title of

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†The term *vascular "spider"* was first used by Patek, Post, and Victor.[28] In addition to the generic words angioma and telangiectasis, this curious arterial aneurysm of the skin has been called spider cancer, naevus araneus (spider web), naevus arachnoideus, tache stellaire, and etoile vasculaire. Arterial or vascular "spider," a purely descriptive name, is the simplest and most satisfactory.

‡Bizarre erythema of the palms and fingers, with or without cyanosis, has been noted in a number of conditions. Osler (Am. J. M. Sc. 152: 187, 1903) saw it in a patient with a fractured skull. A somewhat similar condition may occur in cases of the painful shoulder and hand syndrome which may follow infarction of the heart.[1] The palmar erythema to be described differs from these conditions, as may be seen in the diagrams and photographs.

erythromelalgia. Because of the absence of pain it was obviously not ordinary erythromelalgia. Parkes Weber[5] compared the palms with those which had been noted in 1901 during an outbreak of arsenic poisoning, when the term "arsenical beer drinkers' hands" had been in vogue. It seems to have been painless. Since erythema palmare usually produces no symptoms, there should be no difficulty in distinguishing it from typical acrodynia or erythromelalgia, both of which are, by name and by definition, painful.

The next report, and the one heretofore considered as the original, was made by Lane,[6] in 1929. He studied this phenomenon in two men who had had red palms as long as they could remember. Other members of the families had identical discoloration of the hands. Lane named the condition *Erythema Palmare Hereditarium*, and was the first to point out the hereditary and familial features. From the comments on his paper, and discussions of several subsequent reports, it became clear that many physicians had a vague familiarity with similar cases, but had given the matter no careful consideration.

After Lane's paper, sporadic notes appeared. The syndrome has occurred in association with a multitude of diseases, as shown in Table I. Among the observations which may be of significance, several stand out. Ambler[7] was the first to record the appearance of the syndrome in a previously unaffected patient who developed liver disease. The palmar change persisted for seven years. Ambler measured the skin temperature, and found that it was considerably higher than normal. Mierowsky[8] was the first to observe a similar erythema of the soles in a patient with the palmar change. From the description given by Parkhurst,[9] it does not seem likely that isolated plantar erythema, with sweating and occasionally with eczema, has the same origin, but this must be settled by further study. Slight pain in the hand has been recorded only by Gottron.[10] The pain was atypical, and the red areas were not similar to those of erythromelalgia, as described by Weir Mitchell, in 1872. Clubbed fingers were noted by Bloeman[11] in a patient who had the acquired variety of palmar erythema which had lasted 27 years. Schmidt-La Baume's[12] patient had dermatographism. He also noted accentuation of the redness of his palms after drinking alcoholic beverages. Aguilera Maruri[13] found that the condition in a man with syphilis and tuberculosis gradually cleared up under antisyphilitic therapy, after a known duration of three years. Feldman[14] was the first to point out the association with pregnancy.

Walsh and Becker[15] presented a large series of cases and cited most of the antecedent reports. The thing which excited their attention was the association of palmar erythema and vascular "spiders" in pregnant women, which had never before been reported. Their detailed study included observations of the skin with a capillary microscope and histologic studies of the vascular spiders. Their paper should be con-

sulted by anyone who wishes to obtain a comprehensive grasp of the problem.

The reported cases are tabulated in Table I, along with those to be described later.

MATERIALS AND OBSERVATIONS

The cases we are reporting represent a by-product of the clinical appraisal of cutaneous vascular spiders which has been in progress for several years, and comprises observations on almost 350 cases, of which records have been kept on 251.* Many of the early observations, although made independently, merely served to confirm some of those reported by Williams and Snell[17] and Patek, Post, and Victor,[18] and therefore have not been reported heretofore. A few remarks will help in orientation. We have seen vascular "spiders" appear with liver disease of various kinds. In order of frequency, these are Laennec's cirrhosis, catarrhal jaundice, "cardiac" cirrhosis, obstruction of the bile duct by stone, primary hepatoma, rectal carcinoma with hepatic metastasis, hemochromatosis, jaundice caused by arsphenamine and bismuth, fatty liver, unexplained jaundice, and a case of Weil's disease (probable). Although there was, in these cases, a tendency to chronic hepatic disease, vascular "spiders" occasionally appeared after only a few days of illness. On the other hand, we have seen several instances in which spiders were noted years before signs of liver disease appeared. Judging from the nondescript array of hepatic disorders, the type of disease is of no importance; and, from unpublished observations,[1] it can be stated that, although "spiders" tend to appear in persons with *severe* or *long-standing* liver disease, no known liver function test or clinical feature bears any strict correlation to the development of these vascular lesions. On the average, the worse the liver damage, the greater the likelihood that vascular "spiders" will appear in the skin. Nonetheless, many persons die of liver disease and never have them.

The second group of persons affected with "spiders" consisted of pregnant women. We noted this several years ago, and have observed thirty-seven cases, many of which were seen casually and not followed, since we have not made a routine study of pregnant women. From our records it may be stated that they tend to appear between the second and fifth months of pregnancy, usually increase in size and number until nearly term, and may disappear abruptly within ten days after delivery, although usually the larger ones persist longer and may even become permanent (at least five years). They may reappear or enlarge with subsequent pregnancies. We had supposed that some liver disturbance might explain this phenomenon, but have never found any evidence of past or present hepatic dysfunction that is peculiar to pregnant women who get "spiders," as compared with others who escape these blemishes.

*The early work was done in association with Dr. Donald Forster, and recently with Dr. Morton Hamburger, to whom, along with many house officers and interns, my debt for sundry assistance is very great.

TABLE

NO.	YEAR	AUTHOR	AGE	SEX	RACE	FAMILY HISTORY	VASC. SPIDERS	LIVER DISEASE	PREG-NANCY
–	1899	Chalmers[4]	–	M & F	W	–	–	–	–
1	1929	Lane[6]	51	M	W	+	0	–	–
2	1929	Lane[6]	69	M	W	+	0	–	–
3	1932	Ambler[7]	63	M	W	0	0	+	–
4	1933	Mierowsky[8]	38	M	W	0	0	?+	–
5	1934	Mierzecki[22]	45	M	W	+	0	0	– –
6	1935	Gottron[10]	36	M	W	0	0	?+	–
7	1935	Gottron[10]	26	M	W	+	0	0	–
8	1936	Kerl[23]	45	M	W	+	0	0	–
9	1938	Bloeman[11]	37	M	W	–	0	0	–
10	1939	Schmidt-La Baume[12]	49	M	W	+	0	?	–
11	1939	Aguilera-Maruri[13]	54	M	W	0	0	?	–
12	1939	Feldman[14]	32	F	W	0	0	0	+
13	1940	Navarro-Martin[16]	56	M	W	+	0	0	–
14	1941	Walsh and Becker[15]	26	F	W	0	+	0	+
15	1941	Walsh and Becker[15]	23	F	W	0	+	0	+
16	1941	Walsh and Becker[15]	29	F	W	0	+	0	+
17	1941	Walsh and Becker[15]	31	F	W	+	+	0	+
18	1941	Walsh and Becker[15]	37	F	W	+	0	0	In past
19	1941	Walsh and Becker[15]	36	F	W	+	0	0	In past
20	1941	Walsh and Becker[15]	35	F	W	+	0	0	In past
21	1941	Walsh and Becker[15]	59	F	W	0	0	0	0
22	1941	Walsh and Becker[15]	50	F	W	–	0	?	–
23	1942	This series—Case 1	49	F	W	–	+	+	0
24	1942	This series—Case 2	56	F	W	–	0	+	In past
25	1942	This series—Case 3	40	M	W	0	+	+	–
26	1942	This series	60	M	W	0	+	+	–
27	1942	This series—Case 4	45	M	W	0	+	+	–
28	1942	This series	49	M	W	0	0	+	–
29	1942	This series	43	M	W	0	+	+	–
30	1942	This series	49	M	W	0	+	+	–
31	1942	This series	27	M	W	–	0	?	–
32	1942	This series—Case 5	43	M	W	0	+	+	–
33	1942	This series	36	M	W	0	+	+	–
		Average	45	Male, 20 Female, 13		40%	36%	50%	81% of females

Since we were altogether ignorant of these eruptive spiders in pregnancy, we searched the standard texts on obstetrics, but found no indication of familiarity with this phenomenon. There are, however, numerous reports in dermatology journals, although apparently no one has succeeded in disseminating this information.

The third group consisted of persons who were known to have, or suspected of having, vitamin deficiency diseases. I have records of 120

I

SYPHILIS	SOLES REDNESS	CLUBBED FINGERS	DURATION	REMARKS
–	–	–	–	In white people in tropics.
–	0	0	Life	–
–	0	0	Life	Thrombophlebitis.
0	0	0	7 years	Began after gall bladder disease.
–	+	0	Months	Developed palmar erythema after a wound of the abdomen.
–	+	0	Life	–
–	0	0	– –	Concretio cordis.
–	0	0	Life	–
–	0	0	1 month	Lesions developed while hyperthyroidism was being treated by iodides.
–	0	+	27 yr.	Tuberculous spondylitis.
–	+	0	15 yr.	Dermatographism. Hands had deeper color after ingestion of alcohol.
+	0	0	3 yr.	Tuberculosis and syphilis. The palms gradually cleared after antisyphilitic therapy.
0	0	0	Intermittent	Onset in second and recurrences in 3rd and 4th pregnancy. Fetus had hemorrhages.
?	0	0	Life	Occurred in 3 generations in males only. Onset in 5th month of pregnancy.
0	+	0	Intermittent	Faded after pregnancy, but perceptible 8 months post partum.
0	0	0	Pregnancy	Began in second month of pregnancy and faded by the 9th day post partum.
0	0	0	Pregnancy	Began in the 4th month of pregnancy and was much faded by the 6th week post partum.
–	0	0	Pregnancy	Still present 2 years after pregnancy.
0	0	0	8 yr.	Some pain in hands.
0	0	0	6 yr.	More marked in warm weather.
0	0	0	Life	More marked in warm weather.
0	0	0	6 yr.	Hyperthyroidism.
–	0	0	1 yr.	Hyperthyroidism and diabetes. Palms better after thyroidectomy.
+	–	0	Few wk.	Cirrhosis.
0	–	0	?	Undiagnosed jaundice and hyperthyroidism. ? hepatoma.
0	0	+	Weeks	Cirrhosis.
0	0	0	Weeks	Cirrhosis. Palms faded as jaundice cleared.
0	0	+	2 mo.	Cirrhosis. Mitral stenosis and aortic regurgitation?
0	+	0	Days	Chronic alcohol addiction and lobar pneumonia.
0	+	0	Weeks	Chronic alcohol addiction, lobar pneumonia, and delirium tremens. Palms and spiders faded after pneumonia cleared.
0	0	+	Weeks	Catarrhal jaundice.
0	0	0	Days	Chronic alcohol addiction, jaundice in past. Lobar pneumonia. Color faded after pneumonia was treated.
0	0	+	Unknown	Tuberculous pneumonia, meningitis, epididymitis, and miliary dissemination.
+	0	0	Few mo.	Cirrhosis, proved by autopsy. The palms became red in the last few months of his disease.
14%	20%	15%		

persons with vascular "spiders" who were seen in the Nutrition Clinic in Birmingham, Alabama, during 1940 and 1941. It has not been possible to correlate their occurrence with any known vitamin deficiency syndrome, although, in a few instances, they disappeared after therapy with different vitamin B complex preparations; this may also occur in hepatic cirrhosis.[1] This observation is of questionable significance because the same thing has happened without any therapy or change in

diet, and many "spiders" have persisted in spite of all types of vitamin therapy. They show a notable tendency to occur in children, and there is a strong familial disposition.

Therefore, many or most of those in the third group may rightly belong in the fourth group, which included healthy persons of both sexes and all ages, with no history or suggestion of liver disease, alcohol addiction, pregnancy, or vitamin deficiency. In this normal group it is most difficult to explain the "spiders"; in the other groups there may be a significant common denominator.

From the beginning of this study, very detailed records have been kept on ill persons with "spiders." These include observations on the skin, mucous membranes, and cardiovascular system, and a variety of laboratory studies. Several years ago an example of palmar erythema, associated with vascular spiders and cirrhosis, came under observation and was casually recorded. Not until seeing the second case was our attention sharply focused on the palms. Since then they have not escaped notice, and many patients with other kinds of disease have been inspected for similar changes. In addition to obvious hepatic disease, several instances of palmar erythema have been noted in association with pulmonary disorders, although chiefly among alcohol addicts whose livers were presumably diseased.

The following cases of erythema palmare are presented in detail, so that, if our current interpretations prove erroneous, we shall have clearly defined the background and natural history of the syndrome. It is unfortunate that in the early cases I did not obtain certain details of the history which now seem important. Only after reading the paper of Walsh and Becker[15] was the possible significance of this redness of the hands suspected.

CASE 1 (U-84982).—G. D., a 50-year-old white woman, was admitted to the medical service January 14, 1938, for treatment of pains in the abdomen. She claimed that she had ingested a quart of whiskey daily for twenty years. In recent years she had also taken heroin, and, at the time of entry into the hospital, had been serving a prison term for violation of the Federal Narcotic Law. Her diet should have been adequate, but there were periods when she ate very little. The history was not important in other respects.

Physical examination disclosed a temperature of 98.4° F., a pulse rate of 80, and a respiratory rate of 20 per minute. The blood pressure was 100/65. The enlarged liver presented a smooth, firm border at the level of the umbilicus. It was slightly tender. The spleen was palpable, and its smooth border was a handbreadth below the rib margin. No ascites could be demonstrated. There was no jaundice. The skin of the upper part of the thorax, shoulders, and face was peppered with vascular "spiders;" 43 typical ones were counted. They varied from 5 mm. to 4 cm. in greatest diameter. Dilated vessels were prominent over the nose. The palms showed warm, dusky-red areas, particularly in the hypothenar and thenar regions (Fig. 1). In the red regions the normal pattern of mottling was accentuated, and pale islands stood out against a dark-red, reticulated background.

Chemical studies indicated liver damage. Forty-five per cent of the bromsulphthalein was retained; 3.7 grams of galactose were excreted in testing the

tolerance. The formolgel test was strongly positive. The blood Kahn reaction was strongly positive. The blood cell counts and hemoglobin were normal.

Course.—During her stay in the hospital she became worse, and a new crop of vascular "spiders" appeared. One very characteristic one developed in the site from which another had been removed for histologic study, and several smaller ones appeared, with their centers exactly in the stitch wounds. Later, while she was improving, many of the old and recent "spiders" disappeared and the erythema of the palms faded, but the latter were still more red and warmer than the unaffected adjacent parts. She was discharged after seven weeks; her condition improved considerably during the last month of hospitalization.

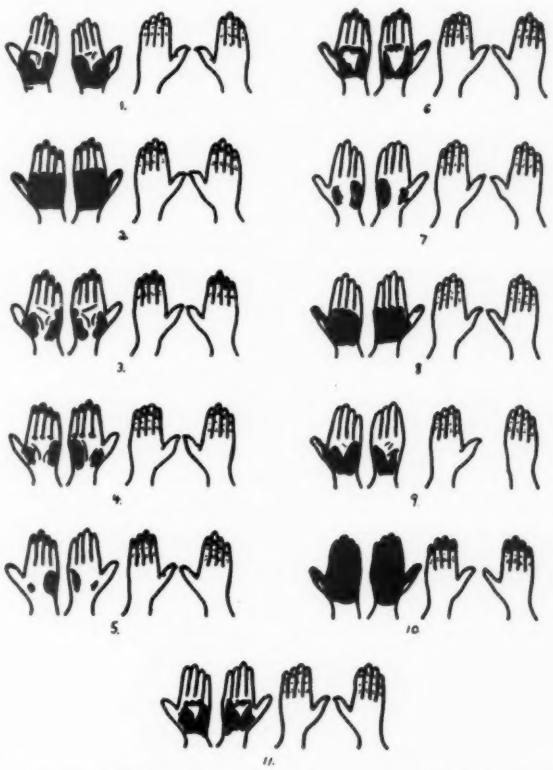

Fig. 1.—Diagrams of the distribution of palmar and digital erythema in the 11 cases. They include Cases 23 through 33 in the table.

Case 2 (U-157095).—E. E., a 56-year-old white woman, was admitted to the medical service April 4, 1941, complaining of weakness and palpitation which had grown worse slowly for at least two years. There was also a history of exertional dyspnea, dry cough, and yellowness of the eyes of long but unknown duration. Her inadequate diet was further curtailed by anorexia, nausea, and soreness of the mouth. Paresthesias of the hands and feet had also been troublesome.

Examination disclosed an emaciated, icteric, white woman whose thyroid gland was enlarged and contained stony-hard nodules. The tongue and lips were cherry red. There was tachycardia, but no fever. The heart was enlarged to the left, and a harsh systolic murmur was heard at the base. Throbbing of the neck vessels was extreme. The arterial pressure was 150/60, and a capillary pulse was detected. Moist râles were heard at the bases of the lungs posteriorly. Below the right costal

margin the sharp edge of the liver was felt readily, and the spleen came down several centimeters, although the abdomen was not distended. Her palms and finger tips were dusky red and warm to the touch. No vascular "spiders" were seen. Moderate edema of the ankles was present.

The icteric index was 39, the serum albumen, 2.5 per cent, the globulin, 3.2 per cent, and the urea nitrogen, 7 mg. per cent. The erythrocytes numbered 3.9 million, and the leucocytes, 7,000; the hemoglobin was 12.2 grams per 100 c.c. The basal metabolic rate was +55 and +38 on two occasions. More than 30 per cent of the bromsulphthalein was retained at 30 minutes. Free hydrochloric acid was present in the fasting gastric juice.

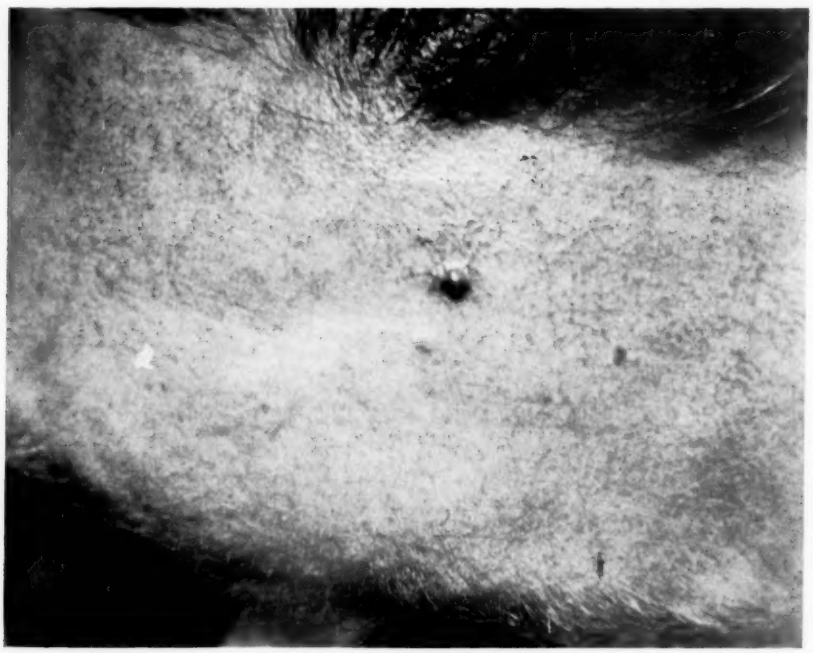

Fig. 2.*—Case 3. This picture shows a large pulsating "spider" which had an elevation of 4 mm. above the surface of the skin of the forehead. In the neighboring regions may be seen the peculiar vascular markings which give the appearance of paper money flecked with silk threads.

Course.—The patient responded to treatment with digitalis, nicotinic acid, thiamin, and riboflavin, although she had auricular fibrillation for several days. The tachycardia persisted, with an average rate of 100 per minute. The administration of Lugol's solution was begun, but, on April 28, she left the hospital because she felt better. Six weeks later she was readmitted in a distressing plight, with edema, dyspnea, and ascites. Her jaundice had increased. On three occasions the serum albumin was 1.5, 1.7, and 0.25 per cent, and the globulin, 6.7, 7.4, and 6 per cent, during the final month. Bone marrow studies suggested a plasma cell myeloma. I did not see her on the second admission, and no note was made about the palms. Her ascites required paracentesis several times. There was gradually increasing liver failure, with deepening jaundice. The prothrombin time was 20 seconds, and the blood urea nitrogen rose to 40 mg. per 100 c.c. She died a month after her second

*The pictures for Figs. 2 and 3 were taken by Mr. J. B. Homan, Associate Professor of Medical Photography, to whom I am greatly indebted for his skill and patience.

admission. The diagnosis was obscure, but the presence of severe liver damage was manifest. No autopsy was done.

CASE 3 (U-165998).—C. B., a 40-year-old white man, a chronic alcohol addict, and a barber by trade, was admitted to the medical service November 2, 1941, complaining of jaundice, edema, swelling of the abdomen, and prostrating weakness which had existed for nearly a month. His diet had been very poor, especially during periodic sprees. He had had a transient spell of painless jaundice at the age of 16. About six months before entry he began to lose energy, and noted edema of the ankles at the end of the day. There was some nausea, particularly in the morning, which he treated by taking a "shot" of whiskey. He had pains and paresthesias in the legs and feet. He stopped work a month before admission, and remained in bed, but the abdominal swelling and jaundice progressed, his urine became dark, and he sought relief in the hospital. The family history was negative; a sister was sure that no one in the family had red hands.

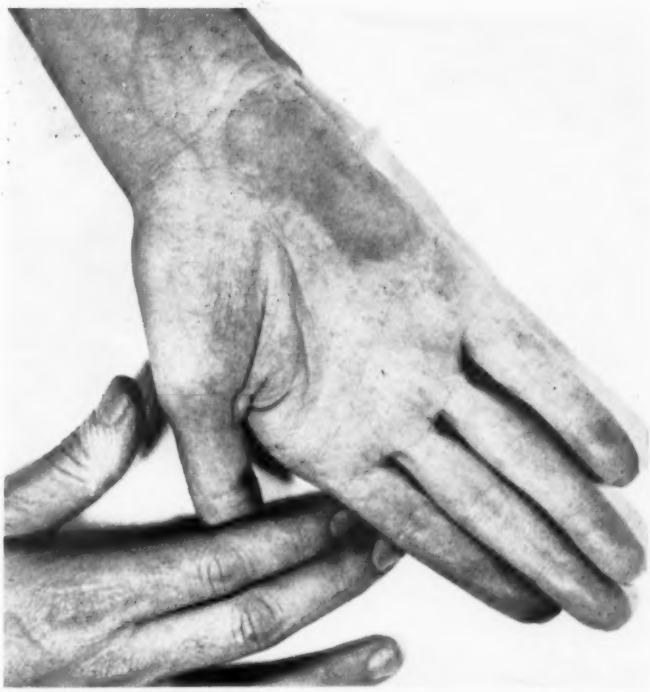

Fig. 3.—Case 3. Palmar erythema is most distinct in the hypothenar area. The sharp but irregular margins are clearly defined. Redness of the terminal phalanges can be made out in the little and index fingers. Mottling of the palm is conspicuous. It will be noted that the erythema is confined strictly to the palmar skin and does not encroach upon that of the wrist.

Physical examination revealed a very ill, deeply jaundiced man; his temperature was 100° F., his pulse rate, 108, his respiratory rate, 22 per minute, and his blood pressure, 140/90. The lips were dusky and the face and chest were warm and moist, and upon the jaundiced skin a dusky red tint was superimposed. There were two, large, pulsating vascular "spiders" (see Fig. 2). Many areas in the skin contained small, dilated arterioles; they were arranged on the chest and abdomen in brushes and chaplets, but had no relationship to the diaphragm or other muscle attachments. In certain regions of the arms there were many similar, short vessels, scattered in disarray which mimicked the apparently aimless pattern of silk threads in American

paper money. The nose also showed tortuous vessels of unusual prominence. There was palmar erythema which was deepest in the hypothenar aspect (see Fig. 3) and dusky red, with irregular, small spots of a paler hue, 2 to 5 mm. in diameter. The red color was present also in the terminal phalanges of all fingers and the thumb, but it cannot be seen clearly in the photograph. There were extreme capillary pulsation in the fingertips, and early clubbing. The chest flared to accommodate the bloated belly, which was well covered with collateral veins. A handsbreadth below the costal margin the firm, nontender edge of the liver was felt. Ascites was present. There was no edema of the legs or ankles, but evidence of peripheral neuritis was found.

The icteric index was 160, and there was a strongly positive direct and indirect Van den Bergh reaction. The prothrombin time was 16 seconds. The blood contained 3.6 units of phosphatase (Bodansky) and 290 mg. of cholesterol per 100 c.c. The erythrocytes numbered 2.6 million, and the leucocytes, 10,000; there were 10.5 gm. of hemoglobin per 100 c.c. Bile was present in the stool and urine.

Course.—The treatment consisted of diuretics, nicotinic acid, thiamin, cod liver oil, and a diet low in fat but high in protein and carbohydrate. It was necessary to resort to abdominal paracentesis Nov. 11 (1900 c.c.), Nov. 16 (3,000 c.c.), and Nov. 20 (1,700 c.c.); there was some seepage from the wound of the second tap. Early vascular changes similar to those in the vascular "spiders" developed about the first paracentesis wound within seven days. The jaundice increased, however, and the patient died on the nineteenth hospital day of hepatic coma. There was no autopsy.

Skin temperature readings were made on the palm at room temperature and at an environmental temperature of 20° C. It was found that the temperature of the areas of erythema ranged from 1.5° to 4.5° higher than the adjacent pale regions of the palm. The temperature of both areas declined and became equal within fifteen minutes after occluding the artery in the upper part of the arm with a pneumatic tourniquet. It was noted that no Bier's spots appeared in the previously red regions, even after forty-five minutes of arterial occlusion. The erythematous skin was more deeply cyanotic than the adjoining skin, and reactive hyperemia was more intense. Temperature measurements over the pulsating vascular "spider" gave readings 2° C. higher than over the neighboring skin; this observation has been made repeatedly on other patients.[1]

Case 4 (U-166406).—L. B., a 45-year-old white man, a chronic alcohol addict, was admitted to the medical service of the General Hospital November 23, 1941, after a convulsion which interrupted a prolonged drinking bout. He had been a heavy drinker since the age of 18, and in recent years had worked in a saloon. He had noticed swelling of his abdomen three weeks before entry, and edema of his ankles developed ten days later. There had been exertional dyspnea. No family history of erythema palmare or telangiectasis could be obtained.

Examination revealed a nervous man who looked older than he admitted being. He was short of breath, and had a warm, moist, cyanotic, yellowish skin. His temperature was 101° F., his pulse rate, 86, his respiratory rate, 28, and his blood pressure, 135/65. The neck veins pulsated. His heart beat was grossly irregular, and the electrocardiogram showed auricular fibrillation. A systolic thrill and the murmurs of aortic stenosis and regurgitation and mitral regurgitation were present, although he did not recall having rheumatic fever. The liver, which was felt with difficulty in his distended abdomen, came down to the umbilicus. Enlargement of the spleen was noted. A few collateral veins stood out on his abdomen. On his chest and shoulders were typical vascular "spiders." His palms and fingertips were involved in the sharply defined, dusky erythema indicated in Fig. 1. There was a mild peripheral neuritis.

The icteric index was 46, the prothrombin time was 21 seconds, and the A/G ratio was inverted (albumin 3.6, globulin 4.0). Examination of the blood showed slight

macrocytosis, but little anemia. Fifteen per cent of the bromsulphthalein was retained after thirty minutes.

Course.—While on the ward his tongue became red, and dermatitis developed on his wrists where shackles had been used. The tongue and skin of the wrists responded to treatment with nicotinic acid, riboflavin, and thiamin, which were used to supplement a diet very high in protein and carbohydrate and low in fat. The jaundice gradually disappeared. The "spiders" on the arms and chest decreased in size, and three disappeared; the erythema of the palms gradually faded until only a faint blush was left in the previously red areas. He was discharged after four weeks.

CASE 5 (U-169539).—J. McG., a 43-year-old white man, was admitted to the medical ward in the last stages of disseminated tuberculosis. There was no story of alcoholism or disease of the liver. He had had the first symptoms of tuberculosis a year previously, and his family physician had found tubercle bacilli in the sputum and cavities in the apices of the lungs. In spite of rest at home, the disease had advanced inexorably. Several months before entry epididymitis set in, and a draining sinus followed. For a few days before admission he was in a deepening stupor.

Examination disclosed signs of widespread pulmonary cavitation, meningitis, and epididymitis. No jaundice was present. The temperature was 102° F., the pulse rate, 150, the respiratory rate, 30, and the blood pressure, 130/104. The fingers were clubbed to an extreme degree, and the erythema of the distal phalanges was extreme. Some osteoarthropathy was present. The palms were universally implicated in the hyperemia. There was one vascular "spider" on the face. Tubercle bacilli in great numbers were found in the sputum.

Course.—After three days in coma he died. The autopsy showed miliary tuberculosis throughout the body, although the liver was not without large areas of normal looking tissue. Much of the lungs had been destroyed.

DISCUSSION

These patients with palmar erythema had diagnostic or presumptive evidence of liver disease. No history of a family tendency to palmar erythema could be obtained, but, since some patients were evasive about the past and vague about the present, this observation is unreliable. The presence of vascular "spiders" in eight cases is of great interest, especially because they tended to wax or wane in phase with the variations in the hyperemia of the hands. There was a definite correlation between the fluctuation in severity of the liver disease, as judged clinically, and the advance or regression of the "spiders" and the palmar erythema. This suggests that whatever evokes or suppresses the one behaves in like fashion towards the other. Together with many other facts, it also points to the probability that a humoral mechanism underlies these two vascular phenomena. In the surveyed cases (excluding those associated with pregnancy), liver disease or a familial tendency to redness of the palms existed; sometimes they occurred together. In some subjects this sign had existed for years, and was unaccompanied by symptoms. In others it appeared after the onset of some illness, perhaps to fade away when health returned.

The nature of this alteration in blood flow in the skin of the hand is obscure. Since it is not necessarily permanent, it undoubtedly consists of a reversible change in local palmar circulatory adjustments. It re-

mains to consider the reasons for the curious localization and the possible cause of the erythema.

Information on the comparative histology of the skin, nerves, and blood vessels of various parts of the palm and sole is scant. It is well known that these regions are more vascular than the neighboring portions of the skin on the arms and legs, but the vascular architecture of different areas of the palm and sole has not been mapped. The presence in the palms and soles of large numbers of direct arteriovenous shunts is significant. Since the increased redness is associated with an increase in surface temperature, the blood flow must be increased. Capillary pulsation, which is so prominent in the finger tips and manifest in the palms, also attests to an open state of the vascular bed in the erythematous region. We have found no increase in the systemic circulation time (decholin) and, with rare exceptions, none in the arterial blood pressure, which indicates that the enhanced blood flow is a local phenomenon and is probably restricted to the skin. A variation in the depth of color from time to time, and the occurrence of a dusky cyanosis on occasions, emphasize the lability of the basic physiologic alteration. According to Walsh and Becker,[15] the overlying skin is not thinner than normal. There is, however, definite dilatation of the palmar capillaries, and many more than the normal number can be seen under the capillary microscope.

The pattern of redness, although the intensity of color fluctuated, was permanent in outline in each of our cases. Among the patients there was much variation in the extent and distribution of the erythema (see Fig. 1). As Chalmers[4] pointed out, no cutaneous nerve supplies the exact area involved. Similarly, the large anastomosing arterial arcades are not limited to the strict confines of the red regions. One must conclude that other local anatomic factors are concerned. Innervation by the sympathetic nerves might possibly explain it, or some structural constant, such as arteriovenous anastomoses, but this cannot be settled on the basis of available data.

The strong thread of familial predisposition stands out. This could mean an inherited structural fault, actual or potential, which allowed the vascular changes to occur under the proper stimulus. Or it might signify unusual susceptibility to the exciting mechanism, a susceptibility perhaps not present in normal persons. The hereditary and familial factors need much more careful study before conclusions may be reached. They were not found in our cases, but the history was not often conclusive. The possible relation to the familial tendency to vascular "spiders" in apparently normal persons[1] should be investigated.

Even if we assume that an anatomic disposition to erythema palmare exists, the exciting cause demands careful scrutiny. Because it and its congener, the cutaneous vascular "spider," vary under the same

clinical influences, we have searched for some physiologic disorder common to both. Study of the vagaries of the vascular "spider," especially the evanescent type which occurs with liver disease and pregnancy, aroused the suspicion that the exciting cause of these eruptive vascular phenomena might be a protracted increase in circulating estrogens or the related 17-ketosteroids. An excess of estrogens is a well-known phenomenon of pregnancy, and it occurs at about the time the "spiders" make their appearance.[1] Not so well known, but nonetheless certainly established, is the fact that the liver normally destroys, changes, or inactivates estrogens.[19] It has been shown that, at least in some cases of cirrhosis, large quantities are excreted in the urine, sometimes in unusual form.[20] Thus the common denominator of acquired vascular "spiders" may reside in prolonged alteration of the circulating 17-ketosteroids; the relationship is certainly quantitative, and perhaps also qualitative, whether in pregnancy or hepatic disease. If this speculation be correct, it is reasonable to assume that the same thing brings out the acquired erythema of the palms in subjects who are predisposed. Lending some weight to this assumption is the observation of Edwards, Hamilton, Duntley, and Hubert,[21] who used the Hardy recording spectrophotometer to study the changes in the concentration of hemoglobin and oxyhemoglobin in the skin of castrate and eunuchoid men before, during, and after treatment with a 17-ketosteroid, testosterone propionate. They obtained objective and quantitative data which verified their clinical impressions concerning the changes in the skin. Of especial interest in connection with our observations on acquired erythema of the hands (and sometimes feet) was their finding that the normally very pale skin of castrates developed a ruddy hue after ketosteroid therapy. The change was particularly marked in the *palms, soles,* and other regions of the skin which are well supplied with arteries. They demonstrated the arterial nature of the blood, with its high content of oxyhemoglobin, and gave reasons for believing that the local blood flow was increased in volume and rate. We have produced evidence that such a state obtains in the red areas of the palms.

The associated clubbing of the fingers in four of our eleven cases deserves comment. In some instances the degree of clubbing varied with the intensity of hyperemia in the finger tips, although the nails changed more gradually than did the digital erythema. The idea that clubbing depends on an increase in blood flow, or a change in the pressure gradient in the arteries, has been suggested in the past. The occurrence of clubbing of the fingers in association with liver and thoracic disease may depend upon the same alterations in circulation which give rise to the palmar and digital hyperemia.

CONCLUSIONS

Study of the acquired vascular "spider" and acquired palmar hyperemia suggests that these vascular alterations are caused by an increase

of the circulating 17-ketosteroids. We assume that the small arteries of susceptible regions of the skin in predisposed persons become widely patent, allowing an influx of arterial blood. In the case of the cutaneous vascular "spider," this may take the form of a small arterial aneurysm. In the palm, general arterial dilatation develops, perhaps with opening of many arteriovenous shunts. We have had no opportunity to study the metabolism of estrogens and related compounds under the circumstances in which these vascular changes occur, but there is ample evidence of an increase in the amount of estrogenic 17-ketosteroids in the blood and urine in liver disease and pregnancy. Because of the elaborate and treacherous technique required, it seemed unwise to undertake assays. We have, however, administered estrogens to some of our subjects whose palms or "spiders" had faded. In two instances the "spiders" reappeared, and in one case the palms became red for the first time.[24] In the absence of any quantitative studies on estrogens, and because the suggestions put forward are supported only by clinical analogy, we hesitate to solidify these ideas into any rigid hypothesis. The pituitary gland has been omitted from consideration altogether, rather from ignorance than belief that it is unimportant. Further implications of this thesis are apparent, and have important bearing upon such phenomena as the association of Hippocratic fingers and digital erythema, the infrequent clinical association of cirrhosis and arteriosclerosis, and other obscure relationships.

SUMMARY

1. The literature on erythema palmare has been reviewed.

2. Eleven new cases are reported in patients with hepatic or pulmonary disease, or both. Contrary to the experience of others, no familial tendency was discovered in these cases.

3. Cutaneous vascular "spiders" occurred in eight of the eleven cases. These lesions waxed and waned concomitantly with the degree of redness of the palms.

4. It is postulated that both of these localized vascular disturbances result from an abnormality in circulating estrogenic substances and other 17-ketosteroids.

5. Experiments to test this hypothesis suggest that it may be valid, although not enough data are available for final conclusions.

REFERENCES

1. Bean, W. B.: Unpublished observations.
2. Dubruilh, W.: Erythema Keratodes of the Palms and Soles, Brit. J. Dermat. 4: 185, 1892.
3. Strachan, H.: Malarial Multiple Peripheral Neuritis, Annual of the Universal Medical Sciences (Sajou's Annual), Philadelphia, Pa. 1: 139, 1889.
4. Chalmers, H. J.: A Symmetrical Palmar Erythema, Lancet 2: 1514, 1899.
5. Weber, F. Parkes: Discussion, Brit. J. Dermat. 26: 165, 1914.
6. Lane, J. E.: Erythema Palmare Hereditarium, Arch. Dermat. & Syph. 20: 445, 1929.

7. Ambler, J. V.: Erythema Palmare Hereditarium, Arch. Dermat. & Syph. **25**: 1156, 1932.
8. Mierowsky, L.: Krankheitsbild des Erythema Palmoplantare symmetricum hereditarium, Arch. f. Dermat. u. Syph. **168**: 420, 1933.
9. Parkhurst, H. J.: Symmetric Erythema of the Soles, Arch. Dermat. & Syph. **40**: 268, 1939.
10. Gottron, H.: Erythema Palmare Hereditarium, Arch. f. Dermat. u. Syph. **172**: 125, 1925.
11. Bloeman, J. J.: Erythema Palmare, Nederl. tijdschr. v. geneesk. **82**: 1519, 1938.
12. Schmidt-La Baume, F.: Zur Kenntnis des Erythema palmoplantare symmetricum hereditarium, Dermat. Wchnschr. **109**: 88, 1939.
13. Aguilera Maruri, C.: Erythema palmare symmetrique, Syphilique? Ann. de dermat. et syph. **10**: 415, 1939.
14. Feldman, S.: Case for Diagnosis (Palmar Eruption Due to Endocrine Disturbances During Pregnancy?), Arch. Dermat. & Syph. **39**: 784, 1939.
Idem: Case for Diagnosis (Inflammatory Papules or Deep Telangiectasia Occurring During the Course of Pregnancy), Arch. Dermat. & Syph. **40**: 1024, 1939.
15. Walsh, N., and Becker, S. W.: Erythema Palmare and Naevus-Araneus-Like Telangiectasis, Arch. Dermat. & Syph. **44**: 616, 1941.
16. Navarro-Martin, A.: Hereditary Symmetric Palmo-Plantar Erythema, Actas dermo-sif. **31**: 178, 1940.
17. Williams, D. H., and Snell, A. M.: Pulsating Angioma (Generalized Telangiectasia) of the Skin Associated With Hepatic Disease, Arch. Int. Med. **62**: 872, 1938.
18. Patek, A. J., Jr., Post, J., and Victor, J. C.: The Vascular "Spider" Associated With Cirrhosis of the Liver, Am. J. M. Sc. **200**: 341, 1940.
19. Israel, S. L., Meranze, D. R., and Johnson, C. G.: The Inactivation of Estrogens by the Liver, Am. J. M. Sc. **194**: 835, 1937.
20. Edmondson, H. A., Glass, S. J., and Soll, S. N.: Gynecomastia Associated With Cirrhosis of the Liver, Proc. Soc. Exper. Biol. & Med. **42**: 97, 1937.
21. Edwards, E. A., Hamilton, J. B., Duntley, S. Q., and Hubert, G.: Cutaneous Vascular and Pigmentary Changes in Castrate and Eunuchoid Men, Endocrinology **28**: 119, 1941.
22. Mierzecki, R.: Erythema Palmo-plantare hereditarium, Zentralbl. f. Haut- u. Geschlectskr. **48**: 280, 1932.
23. Kerl, W.: Erythema palmare hereditarium, Wien. med. Wchnschr. **86**: 705, 1936.
24. Bean, W. B.: A Note on the Development of Palmar Erythema and Vascular "Spiders" in Cirrhosis of the Liver and Their Development Following the Administration of Estrogens, Am. J. M. Sc. **204**: 251, 1942.
25. Perera, G. A.: A Note on Palmar Erythema (So-Called Liver Palms), J. A. M. A. **119**: 1417, 1942.

ADDENDUM

In a discussion of my paper on Vascular Spiders and Palmar Erythema at a meeting of the Central Society for Clinical Research, Chicago, Ill., Nov. 6, 1942, Lt. Col. P. S. Hench called attention to his work on the ameliorating effect of jaundice and pregnancy upon certain forms of arthritis, and suggested that a similar mechanism might underlie this phenomenon and the emergence of "spiders."

PATHOGENESIS OF SUBACUTE BACTERIAL ENDOCARDITIS

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SUBACUTE bacterial endocarditis was first described in this country as a clinical entity by Libman[1] at about the same time that Schottmüller[2] recognized it abroad. As early as 1909-10, Libman and his associates, notably Celler[3] and Baehr,[4] made thorough pathologic, bacteriologic, and clinical studies which elucidated the salient features of the malady and permitted its early clinical recognition.

Because the disease is insidious, Schottmüller named it *endocarditis lenta*, and stated that the *Streptococcus viridans mitis* is the sole cause of the infection. It is agreed that in the majority of cases the *Streptococcus viridans* is the direct etiologic factor. However, as was first pointed out by Libman and his co-workers, and later universally confirmed by Herrick,[5] Hamman and Rich,[6] Thayer,[7] and Horder,[8] it is now known that other microorganisms can be responsible for this form of endocarditis. Not only can any microorganism produce the disease, but not infrequently two or three different bacteria may be recovered from blood cultures and from the diseased valve. Orgain and Poston[9] described five cases of mixed infection in bacterial endocarditis. The individual cases recently described (De La Chapelle and Graef,[10] Spink and Nelson,[11] Weehsler and Gustafson[12]), in which the endocarditis was caused by the Brucella organism, indicate that the rarest types of microorganisms may also cause subacute bacterial endocarditis. It is therefore appropriate to adhere to the name proposed by Libman, i.e., *subacute bacterial endocarditis*.

The most thorough investigation of the pathogenesis of the disease has failed to yield the answers to many fundamental questions. Why does subacute bacterial endocarditis affect only a diseased valve? Why does the damaged valve often enjoy immunity from the disease for many years, and then suddenly become vulnerable? Why does the disease last so long, and why does it almost always end fatally?

It has been assumed by the older classical theorists that the illness is protracted because the *Streptococcus viridans* is less virulent than most other pathogens. A priori, this does not appear reasonable, for other microorganisms, as stated above, which are otherwise very virulent, such as the *Streptococcus hemolyticus*, the gonococcus, the pneumococcus, the meningococcus, and Friedländer's bacillus, can cause the same pathologic changes in the valves and the same drawn-out clinical course. On the other hand, the *Streptococcus viridans* may cause *acute* fulminating endocarditis, with death in two to seven weeks, as in the case of four

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patients at the Beth Israel Hospital[13] who were weakened by serious previous illnesses. The virulence of the organism appears, therefore, to be a much less important factor than the natural resistance of the host.

Another view of the pathogenesis of this disease was expressed by Clawson and Bell,[14] who are of the opinion that rheumatic endocarditis and subacute bacterial endocarditis are merely mild and severe forms, respectively, of the same infection. Von Glahn and Pappenheimer[15] added support to this view by their contention that subacute bacterial endocarditis is usually implanted on recently active rheumatic lesions, and not on old or healed rheumatic valvular defects. To refute this concept of the pathogenesis of subacute bacterial endocarditis, we need only consider that the influenza bacillus, the pneumococcus, the gonococcus, and numerous other organisms can cause the disease, and surely these organisms have no relationship to rheumatic fever. Furthermore, in the majority of cases there is no pathologic evidence in the myocardium, such as the presence of Aschoff bodies, or in the pericardium, of recent rheumatic infection. Of course there is no doubt that rheumatic valvular disease is a vital predisposing factor, but its immediate relation to subacute bacterial endocarditis is undoubtedly the exception rather than the rule. It is also well known that, occasionally, syphilitic aortic valvular disease may be the forerunner of subacute bacterial endocarditis, and congenitally deformed valves likewise predispose to this fatal infection. As far as is known, congenital valvular defects are certainly not the result of rheumatic infection.

Grant, et al.,[16, 17] and Keefer[18] have advanced the theory that platelet thrombi on the previously damaged heart valve serve as a nidus on which the bacteria deposit themselves, thrive, and initiate subacute bacterial endocarditis; they assume that, in order that bacteria may lodge on the previously diseased, deformed valve, a thrombotic valvular lesion must pre-exist. Despite the plausibility of such a concept, we are confronted with the following questions: (1) What is the original cause of such blood platelet thrombi, and (2) why do they occur in some cases of damaged valve and not in others? Furthermore, what is the origin of such blood platelet thrombi in a congenital heart lesion or on a congenitally bicuspid aortic valve? We know that, at autopsy, in the majority of cases of congenital heart disease and recurrent endocarditis and heart failure, no thrombotic lesions are seen, and terminal thrombotic endocarditis is quite common in wasting diseases and other agonal states, but subacute bacterial endocarditis does not occur in these cases. Furthermore, subacute bacterial endocarditis does not superimpose itself on the thrombotic endocarditis described by Friedberg, et al.*[19] Therefore, why should we assume that a thrombotic lesion

*Recent studies in the laboratory of Dr. Paul Klemperer, Mt. Sinai Hospital, N. Y., by Dr. Arthur C. Allen, show definitely that what is called thrombotic endocarditis is pathologically not thrombotic because blood platelets and fibrin are conspicuously absent. The lesion, as shown by Allen, is a degenerative endocardial change; similar areas are found also in the myocardium in chronic wasting diseases and terminal infections.

exists on some rheumatic valves and not on others? It is more reasonable to assume that, in subacute bacterial endocarditis, if section shows some thrombosis along the edge of the valve, this is only part of the active pathologic process, and not the pre-existing cause.

It seems to us that the peculiar pathologic changes and clinical course of this disease can be attributed to local tissue reactivity caused by hyperimmunity. The local and systemic tissue resistance and the immunity of the reticuloendothelial system in general, and of the endothelium of the valves and heart in particular, are responsible for the protracted course. Death occurs only when there is exhaustion of the endothelial system, unless some complication, such as embolism, or rupture of a mycotic aneurysm in the brain or in the subarachnoid space, terminates the disease earlier. The endothelial nature of the disease thus asserts itself. So prominent is the invasion of the endothelial system in this disease that one may even speak of it as infectious endotheliosis, in analogy to what E. Frank terms, among the diseases which manifest a hemorrhagic diathesis, "hemorrhagic endotheliosis."

That the reticuloendothelial system plays an immense role in the production of immunity was well established by the studies of Metchnikoff, Aschoff, Goldmann, Ehrlich, and others. Recently, Sabin,[20] in a brilliant piece of work, demonstrated microscopically the formation of antibody globulin in the cells of the reticuloendothelial system, which emphasizes the prime importance of the endothelial cell in resisting infection. The body reaction to infection is thus determined largely by the state of the reticuloendothelial system, and can be conveniently classified, as Siegmund[21] and Dietrich[22] suggested, into three general types: the a-reactive, the normally reactive, and the hyperreactive. In the a-reactive type, which occurs with fulminating infections, there is complete loss of reactivity, so that any microorganism in an insignificant focus may so overpower the body as to cause death without localization of the infection at the focus, and before any appreciable pathologic change can occur ("cryptogenetic sepsis"). In contrast to this, in the normally reactive type of infection, the immunity of the body permits localization of the infection. In the hyperreactive, the tissues have become highly immunized against a microorganism, and there is a marked local reaction at the site of invasion, with the advantage in the struggle largely on the host's side. We believe that this last type of reaction, i.e., that of tissues highly immunized by previous infection, explains the lesions and clinical course of subacute bacterial endocarditis. If the lesions were not located in the heart, whence broken-off vegetations are carried to distant parts of the body, either with or without bacteria, the outcome would not necessarily be fatal. When considered as a hyperimmune reaction to infection, the pathologic changes responsible for the symptoms in this disease can be easily understood. We shall attempt to review them in this light, one by one.

The disease begins during the transient bacteremia that accompanies most infections (pyelitis, tonsillectomy, extraction of an infected tooth, etc.), affecting first the capillaries of the valve. Because of the hyperimmunity and increased local resistance in chronically diseased valves, the usual response to infection, such as exudation of leucocytes, ulceration, and connective tissue formation, does not occur, but, instead, there is a deposit of fibrin and blood platelets similar to that which follows a clean skin incision. This fibrin, blood platelet thrombus constitutes the soil on which the circulating bacteria implant themselves. Polypous vegetations form and tend to remain localized or spread by contiguity to different parts of the heart—in mitral stenosis, to the auricle, and, in aortic disease, to the ventricle, or even to another valve.

In contradistinction to the theories of the above mentioned authors, and particularly that of Keefer, who considers the thrombotic lesion to be the primary factor, it is our concept that the thrombus is caused by the action of the bacteria on the capillaries of the diseased valve, and that it is from these capillaries that the blood platelets and fibrin escape. On this thrombus more bacteria deposit themselves, forming additional vegetations. Thus a septic focus develops on the heart valve, which, as a rule, gives rise to secondary foci in other parts of the body. Following this viewpoint, we may say that *subacute* bacterial endocarditis constitutes an "endocardial sepsis," whereas *acute* ulcerative endocarditis can be termed "septic endocarditis." In the latter, pathologic changes in the endocardium are a part of those in the rest of the body; whereas, in the former, all the changes that take place in the rest of the body are caused by the original focus in the endocardium. The changes in the capillaries and arterioles, as well as those which occur occasionally in the larger blood vessels, are caused either by direct embolism from the endocardial vegetations, with or without bacteria, or by toxins. In either event, aneurysmal dilatation and rupture of small capillaries or arterioles may result. In other instances, vascular obstruction may occur, e.g., in the larger vessels of the lower extremities, leading to gangrene, or sudden obstruction, by bacterial emboli, of the coronary or mesenteric vessels. Aneurysmal dilatation in the brain may lead to cerebral or subarachnoid hemorrhage.

Since the embolus usually comes from the left side of the heart, pulmonary infarction does not often occur, but renal and splenic infarction is common. The truly bacterial emboli have a tendency to involve the larger blood vessels (arterioles), whereas the toxins tend to affect the capillaries. In most instances the petechiae are caused by the impairment in the permeability of the capillaries which results from the toxic effect of the bacteria.

The manifestations of embolism depend largely on the size of the vessel. If it is in small capillaries (as the conjunctivae), it causes the characteristic white-centered petechiae, whereas in larger vessels it forms little nodes (Osler nodes) which have a great tendency to be

absorbed. When it attacks the endothelial layer of the glomerulus, it causes the characteristic Lohlein-Baehr glomerulonephritis. This is a progressive kidney lesion which shows, as is the case in all other organs, no tendency to connective tissue formation. Since neither the afferent or efferent vessels of the kidney suffer, there is no increase in blood pressure. The pin-point hemorrhages in the glomeruli give rise to the typical "flea-bitten" kidney. Christian[23] reported studies on the kidneys of sixty-one patients who died from subacute *Streptococcus viridans* endocarditis. He found areas of infarction in 91.8 per cent, proliferative, cellular, glomerular lesions which were analogous to the lesion in acute intracapillary proliferative glomerulonephritis in 80.32 per cent, and diffusely distributed, hyaline thickening of the walls of the glomerular capillaries in 16.39 per cent. He encountered five types of glomerular lesions: (1) proliferation of the capsular epithelium, (2) focal fibrous lesions, (3) complete disorganization of glomeruli, (4) hyalin fibrinoid thrombi in glomerular vessels, and (5) masses of bacteria in glomerular capillaries.

In short, this is a disease which, either by bacterial vegetations or toxins, affects first the endothelium of the endocardium and valves, and then the endothelial structures of capillaries and arterioles of different parts of the body. The outcome of the disease can be explained by the degree of that invasion.

In the majority of cases there is mild sepsis. The patient is not "heart-conscious." Only because of the protracted fever, the presence of valvular disease, and the moderate anemia does the physician suspect the possibility of this disease. In the majority of cases our attention is called to involvement of the capillaries by the petechiae in the conjunctivae, mouth, or elsewhere. In the finger tips there may be the painful Osler nodes (known also as Libman nodes). In most cases the endothelial system of the spleen responds actively, so that there are enlargement and induration of this organ. In acute infections, on the other hand, the spleen is soft and tender.

Another early and frequent manifestation is hematuria. Although this accompanies gradually increasing involvement of the glomerular capillaries, it is usually associated with very little albuminuria, only occasional casts, and no change in the specific gravity; usually, there is no increase in the blood pressure.

In many cases, clubbing of the fingers develops quite rapidly as a result of capillary changes in the nail bed. When the disease is protracted, the endothelium of the hemopoietic system (bone marrow, etc.) is involved. As in subleucemic leucemia, there may be leucopenia, with immature leucocytes (myelocytes and myeloblasts) in the blood.

There is every reason to believe that, in some cases, healing and recovery occur, as Libman has reported. When blood cultures are taken often enough in the acute phase of the disease, the organism will be found in more than 90 per cent of the cases (Libman and

Friedberg[24]). The degree of bacteremia, that is, the number of colonies found on culture, does not indicate how soon the disease will end fatally, although in the terminal stage the number of colonies increases rapidly. There are on record a number of cases of two or three years' duration in which there were numerous colonies in the blood culture. On the contrary, in the healed stage (Libman), when the blood cultures are persistently negative and even when no bacteria are found in the diseased valve post mortem, there may be marked anemia and uremic manifestations caused by diffuse glomerular disease, but no increase in blood pressure.

The disease occurs typically in patients with rheumatic heart disease who, after the original infection, apparently acquired enough immunity to insure against reinfection. In contrast to other cases of rheumatic fever, in most of the cases of subacute bacterial endocarditis recurrent rheumatic endocarditis is the exception. It is also important that, even during the first acute attack of rheumatic fever, such patients have very few cardiac manifestations, so that sometimes the patient cannot recall having been afflicted with valvular disease, unless his attention had been called to the existence of a murmur. Neither the myocardium nor pericardium was involved, and therefore there were no cardiac symptoms. This is also the reason why, in these cases, a history of congestive heart failure is rare, nor does it occur in patients with auricular fibrillation. One encounters cases in which there is no history of rheumatic fever, although, in his youth, the patient may have had mild growing pains in the muscles or extremities, or, after a mild attack of scarlet fever or pneumonia, may have been left with a valvular lesion which produced no important symptoms. There are exceptional cases, as, for instance, those reported by Grossman and Lieberson[25] and Segal,[26] in which auricular fibrillation and subacute bacterial endocarditis coexisted. We believe that, in these cases, as a rule, congestive heart failure does not account for the fibrillation, but that the vegetation invades the mural endocardium of the auricle, causing fibrillation without signs of congestive heart failure.

If there is increased resistance and hyperimmunity in these cases, what permits the subacute bacterial infection to start on the diseased valve? We feel that the insidiousness of the disease indicates that some other infection acts as a forerunner for subacute bacterial endocarditis. There is often an upper respiratory infection caused by the influenza bacillus or pneumococcus, during the course of which the *Streptococcus viridans,* which is found so widely distributed in the body, enters the blood stream, lodges on the diseased valve, and forms the nidus of the subacute infection. It is known, further, that, after tonsillectomy, cystoscopy, or extraction of an infected tooth, there is often a transient bacteremia which may do no harm to the normal person, but, when a valvular lesion is present, the circulating bacteria may lodge on the valve and start the infection. Such a concept suggests that, if we attack

the disease in its very early stage with chemotherapeutic measures, as recently suggested by Christian, we may be able to abort it. Ordinarily, one sees the patient late in the course of the disease, when the endothelial system and other organs are so affected that the chemotherapeutic agent cannot reach all the bacteria and may do more harm than good. Our hope lies in discovering the disease early, before the endothelial system has become irreversibly exhausted, and before complications have set in.

SUMMARY

Subacute bacterial endocarditis is a distinct pathologic and clinical entity. The vegetative endocarditis that characterizes this disease, with its exudation of fibrin, blood platelets, and enmeshed bacteria, represents a state of high local and general tissue immunity to bacterial invasion, rather than lowered resistance; the immunity resides in the local endothelial structures, as well as in the general reticuloendothelial system. Since the reaction to this bacterial invasion is largely endothelial, the disease can rightfully be termed *infectious endotheliosis*.

Subacute bacterial endocarditis occurs typically in patients who have valvular disease, usually rheumatic, but who have acquired a high degree of immunity, so that reinfection, recurrent endocarditis or pancarditis, and congestive heart failure do not occur. This increased immunity is responsible for the fact that the patient is not heart-conscious even during the attack of acute valvular infection. Then a transient bacteremia, caused by an upper respiratory infection, tonsillectomy, the extraction of an infected tooth, or pyelitis, permits secondary invasion and implantation of bacteria (usually the ubiquitous *Streptococcus viridans*) on the damaged valve. A careful history will reveal that some infection which lowered the general body resistance is usually the beginning of an illness that later develops into subacute bacterial endocarditis. Although the bacteria are able to implant themselves on the damaged valves, they find in the valve an altered tissue reactivity which does not permit much local damage, such as ulceration or extension into the myocardium or pericardium. A more favorable outcome would be likely if the bacteria were not localized in a focus that communicates directly with the blood stream. If embolism does not cut the disease short, death occurs when the local and systemic endothelial systems become exhausted.

Subacute bacterial endocarditis is a true endocardial sepsis, for the valve acts as the primary distributing focus of the infection. As such, if the focus can be removed surgically (as in some cases of patency of the ductus arteriosus) or chemotherapeutically before complications set in, there is some hope for a cure of this dreaded disease.

REFERENCES

1. Libman, E.: On Some Experiences With Blood Cultures in the Study of Bacterial Infections, Bull. Johns Hopkins Hosp. **17**: 215, 1906.
2. Schottmüller, H.: Die Artunterscheidung der für den Menschen pathogenen Streptokokken durch Blutagar, München. med. Wchnschr. **50**: 849, 1903.

3. Libman, E., and Celler, H. L.: The Etiology of Subacute Infective Endocarditis, Am. J. M. Sc. **140**: 516, 1910.
4. Baehr, G.: Glomerular Lesions of Subacute Bacterial Endocarditis, Am. J. M. Sc. **144**: 327, 1912.
5. Herrick, J. B.: The Healing of Ulcerative Endocarditis, Med. News **81**: 433, 1902.
6. Hamman, L. V., and Rich, A. R.: Two Cases of Subacute Bacterial Endocarditis, Internat. Clin. **2**: 201, 1933.
7. Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis, Johns Hopkins Hosp. Reports **22**: 1, 1926.
8. Horder, T. J.: Infective Endocarditis With an Analysis of 150 Cases and With Special Reference to the Chronic Form of the Disease, Quart. J. Med. **2**: 289, 1908.
9. Orgain, E. S., and Poston, M. A.: Mixed Infections in Bacterial Endocarditis, Am. Heart J. **23**: 6, 823, 1942.
10. De La Chapelle, C. E., and Graef, I.: Occurrence of Subacute Bacterial Endocarditis in Mitral Valvular Disease With Pre-existing Auricular Fibrillation. A Case Report, Am. Heart J. **8**: 352, 1932.
11. Spink, W. W., and Nelson, A. A.: Brucella Endocarditis, Ann. Int. Med. **13**: 721, 1939.
12. Wechsler, H. F., and Gustafson, E. G.: Brucella Endocarditis of Congenital Bicuspid Aortic Valve, Ann. Int. Med. **16**: 6, 1228, 1942.
13. Held, I. W., and Goldbloom, A. A.: Acute Streptococcus Viridans Endocarditis—Report of Four Cases With Autopsy Observations in Two, Arch. Int. Med. **53**: 508, 1934.
14. Clawson, B. J., and Bell, E. T.: A Comparison of Acute Rheumatic and Subacute Bacterial Endocarditis, J. A. M. A. **37**: 66, 1926.
15. Von Glahn, W. C., and Pappenheimer, A. M.: Relationship Between Rheumatic and Subacute Bacterial Endocarditis, Arch. Int. Med. **55**: 173, 1935.
16. Grant, R. T., Wood, J. E., and Jones, T. D.: Heart Valve Irregularities in Relation to Subacute Bacterial Endocarditis, Heart **14**: 247, 1928.
17. Grant, R. T.: Observations on Endocarditis, Guy's Hosp. Rep. **86**: 20, 1936.
18. Keefer, C.: Pathogenesis of Bacterial Endocarditis, Am. Heart J. **19**: 352, 1940.
19. Friedberg, C. K., Gross, L., and Wallach, K.: Nonbacterial Thrombotic Endocarditis Associated With Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread vascular Lesions, Arch. Int. Med. **58**: 662, 1936.
20. Sabin, F. R.: Cellular Reactions to Dye-Protein With Concept of Mechanism of Antibody Formation, J. Exper. Med. **70**: 67, 1939.
21. Siegmund, H.: Untersuchungen über Immunität und Entzündung, Verhandl. d. deutsch. path. Gesellsch. **19**: 114, 1923.
22. Dietrich, A.: Die Reaktionsfähigkeit des Körpers bei septischen Erkrankungen in ihren pathologisch-anatomischen Aeusserungen. Verhandl. d. Gesellsch. f. inn. Med. **37**: 180, 1925.
23. Christian, H. A.: Kidneys in Subacute Streptococcus Viridans Endocarditis, J. Mt. Sinai Hosp. **8**: 427, 1942.
24. Libman, E., and Friedberg, C. K.: Subacute Bacterial Endocarditis, New York, 1941, Oxford University Press.
25. Grossman, A., and Lieberson, A.: Unusual Clinical Manifestations of Subacute Bacterial Endocarditis, Am. Heart J. **14**: 352, 1937.
26. Segal, M. S.: Auricular Fibrillation and Auricular Flutter in the Subacute Bacterial Endocarditis, New England J. Med. **212**: 1077, 1935.

THE ROLE OF INSULIN-FREE, HISTAMINE-FREE PANCREATIC TISSUE EXTRACT IN THE TREATMENT OF PERIPHERAL ARTERIAL DISEASE*

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In 1928, Frey and Kraut[1] described a physiologically active substance which is excreted in the urine and is normally present in large quantities in the pancreas. The intravenous administration of this material to animals produced a transitory fall in blood pressure, an increase in the cardiac rate, and an increase in the stroke volume. Gley and Kisthinios,[2] working independently, isolated an insulin-free material from the pancreas which had the property of producing a transitory fall in blood pressure after intravenous administration, and also antagonized the pressor effects of epinephrine. In neither case could the physiologic effect be attributed to histamine, choline, or peptone. This question has been raised by Villaret, Justin-Besançon, and Cachera,[3] who felt that the crude preparations with which they were working contained a sufficient quantity of choline and histamine to account for the cardiovascular action. More recently, Elliot and Nuzum,[4] using a more highly purified preparation, were able to demonstrate that the physiologic activity of their material was not due to the presence of histamine, choline, or peptone.

Wolffe and his co-workers,[5] because of certain superficial similarities between the action of this type of pancreatic tissue extract and the so-called heart muscle extract, suggested that the activity of the former might be attributed to the presence of adenosine, adenylic acid, or some allied substance. Both adenylic acid and adenosine, in addition to a transitory fall in blood pressure and an increase in coronary flow, cause transitory heart block when administered intravenously. This last action is so uniform that Drury and Szent-Györgyi[6] suggested that it be used as a biologic method of identification of these substances. We have administered the pancreatic extract to be described, in doses as high as 100 units, intravenously to dogs, without producing heart block. Similar negative observations were made on anesthetized guinea pigs. This is in accord with the observations of Elliot and Nuzum[4] on rabbits and guinea pigs.

Clinically, the material has been used widely. Vaquez, Giroux, and Kisthinios[7] and Wolffe[8] have reported favorable results in the treat-

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ment of angina pectoris. The European literature contains a considerable volume of confirmatory clinical observations, but much of this is based on symptomatic relief of ill-defined clinical entities.

Wolffe and Digilio[9] analyzed a series of 108 patients with hypertension who were treated with a similar pancreatic tissue extract. Less than 8 per cent of the group showed any significant lowering of the systolic and diastolic blood pressure after medication; more than 60 per cent, however, showed symptomatic relief which persisted for more than a year. Fisher, Duryee, and Wright,[10] working with a carefully studied series of cases of clearly defined vascular disease, under controlled experimental conditions, were able to show that such tissue extracts materially prolonged the time required for the onset of claudication when the patients were subjected to standardized physical exertion.

During the course of the last few years the original methods for the extraction and isolation of the active principle have been so improved that a highly potent, stable preparation has been made available.* This material, which will be described in detail elsewhere,[11] was prepared by a modification of the process used by Werle and Urhahn,[12] and contains approximately 15,000 units per gram. Lyophilized preparations lost no activity after being kept at 37° C. for a period of two hundred seventy days.

Finely-ground, fresh or frozen hog pancreas is suspended in water, the pH of the mixture is adjusted to 8.0, and the mixture is digested with trypsin at 37° C. Toluene is used as a preservative. The trypsin destroys all the insulin in the suspension. The mixture is then acidified with trichloracetic acid, and ammonium sulfate is added to one-third of saturation. The insoluble matter, which consists of fibrous tissue, fat, undigested proteins, (primary) proteoses, and trypsin, is centrifuged off and discarded. The clear, supernatant solution is then brought to saturation with ammonium sulfate, and the crude precipitate formed thereby is centrifuged off. (The saturated ammonium sulfate mother liquor retains peptones, amino acids, and any histamine or choline which may be present.) The crude precipitate is then dialyzed under toluene in cellophane tubes against distilled water until it is free of sulfate (dialysis effects the removal of ammonium sulfate and of any histamine or choline which may have been adsorbed on, or included with, the crude precipitate). The water is finally removed by the Niphanoid process (dehydration of frozen extract under high vacuum).

Standardization.—In our experience, neither the procedure of Gley and Kisthinios[2] nor that of Frey and Kraut[1] is dependable for the assay of the active principle. In the first instance, the unit was considered that quantity which, when injected intravenously into a 2.0 kg. rabbit, caused a barely perceptible fall in the blood pressure; in the second instance, it was defined as that amount which caused an increase in the amplitude of cardiac contraction of one minute's duration. We encountered such wide variations in potency with both of these methods of biologic assay that we felt the need of devising one which would be more reliable. In our experience, the most dependable animal for this procedure is the dog. The unit, as we define it, is that quantity of the active principle which, when injected intravenously into an atropinized dog under sodium barbital anesthesia, will exactly counteract the pressor effect of a minimal hypertensive dose of epinephrine. Since

*Tissue extract—P-415—obtained from the Research Laboratories, Winthrop Chemical Company, Inc., Rensselaer, N. Y.

dogs under comparable conditions vary widely in their vasomotor response to epinephrine, this minimal hypertensive dose must be established for each animal. We have found that the required amount varies between 15 and 50 micrograms for dogs of 10 to 15 kg., although the dose is not proportional to the weight. It should also be pointed out that this minimal hypertensive dose varies with the tone of the vasomotor system. Large or repeated doses of the tissue extract depress the tone of the peripheral vasomotor system, as indicated by alteration of the threshold dosage of epinephrine. Successive doses of one or more units of this extract should therefore be spaced at intervals of at least fifteen minutes in order to allow for recovery. In practice, this factor is largely corrected by allowing a sufficient period to elapse so that the threshold for normal epinephrine responses (indicative of a normal autonomic equilibrium) is re-established. Three animals are used for each assay. The standard unit may be defined as that quantity of the extract which will neutralize the pressor effects of 30 micrograms of epinephrine.

EXPERIMENTAL OBSERVATIONS

1. Dogs. All observations were made on atropinized dogs under sodium barbital anesthesia. The intravenous administration of the active principle in small doses (1 to 2 units) produces a transient fall in the blood pressure, of the order of 30 to 45 mm. Hg, which persists for about ten minutes. This fall in blood pressure is accompanied by a marked increase in pulse pressure, and, as indicated by Greene,[13] this effect is associated with marked coronary dilation. Using a constant temperature plethysmograph and a photoelectric recording system, which are described in detail below, we have been able to demonstrate that the initial fall in blood pressure is accompanied by a marked increase in limb volume, and that this increased volume is still evident long after the initial blood pressure level is re-established. A sharp fall in blood pressure follows the intravenous administration of 2 units of the active principle, and with this there is an increase in pulse pressure (Fig. 1). This occurs immediately after administration; the normal level is re-established within nine minutes. Below this there is a simultaneous record of the changes in limb volume. The first part of this record shows the normal volume; the second portion of the record starts at the time of injection, and shows the increased volume associated with the fall in blood pressure. This increased volume persists long after the blood pressure has returned to its normal level; the third portion of the record, which was made fifty minutes after the injection, shows that the peripheral dilatation is still present.

When the active principle is administered intramuscularly, there is no appreciable effect on the blood pressure. Giving doses as large as 80 units to a 15 kg. dog produced no fall in blood pressure over a period of seventy-five minutes. However, such doses produced a persistent increase in limb volume. Fig. 2 shows this clearly. The intramuscular administration of 20 units of the active principle failed to produce any demonstrable change in the blood pressure of a lightly anesthetized dog. The injection, however, was associated with a prompt increase in limb volume which persisted for a period well in excess of thirty minutes.

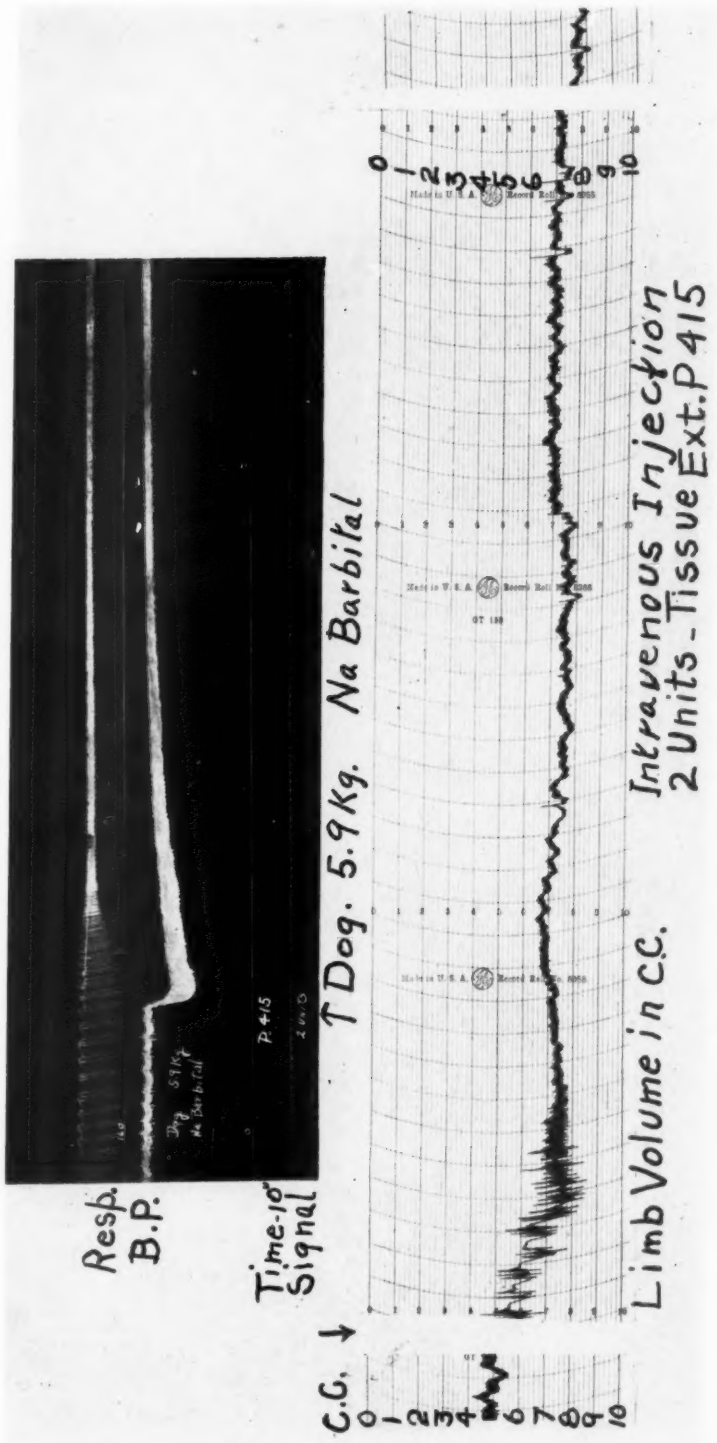
Resp.
B.P.
Time-10"
Signal
C.C.
Limb Volume in c.c.
↑ Dog. 5.9 Kg. Na Barbital
Intravenous Injection
2 Units - Tissue Ext. P 415
P 415

Fig. 1.

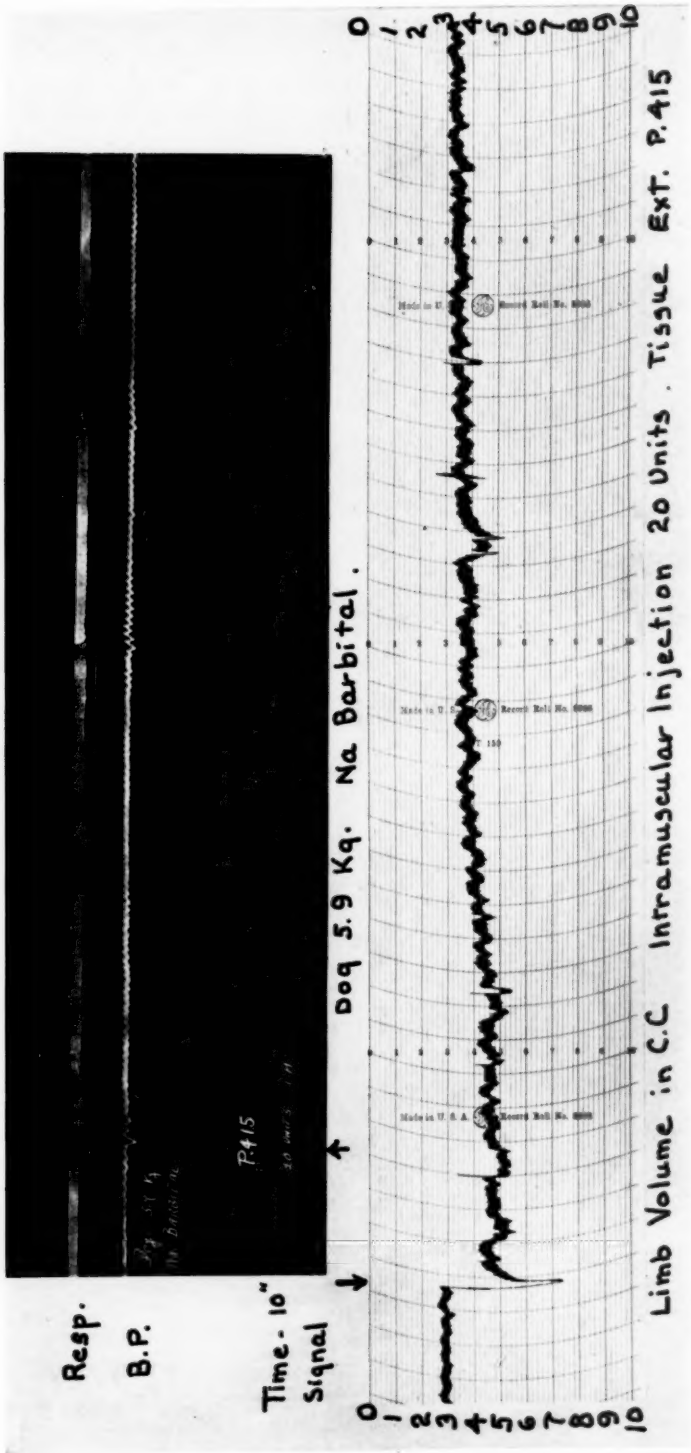
Resp.
B.P.
Time - 10"
Signal
P.415
Dog 5.9 Kg. Na Barbital.
Limb Volume in C.C
Intramuscular Injection 20 Units . Tissue Ext. P.415
0 1 2 3 4 5 6 7 8 9 10

Fig. 2.

2. Isolated Smooth Muscle.—Using the isolated rabbit ileum in oxygenated Ringer-Locke solution, we have been able to show that the addition of the active principle to the bath will produce relaxation, as indicated by a diminution in the tonus of the preparation. Neither the rate nor the amplitude of contractions is materially altered, but a reversible inhibition of tonus is demonstrable when 5 units are added to a 50 c.c. bath. Removing the active principle from the bath immediately causes restoration of normal tonus (Fig. 3).

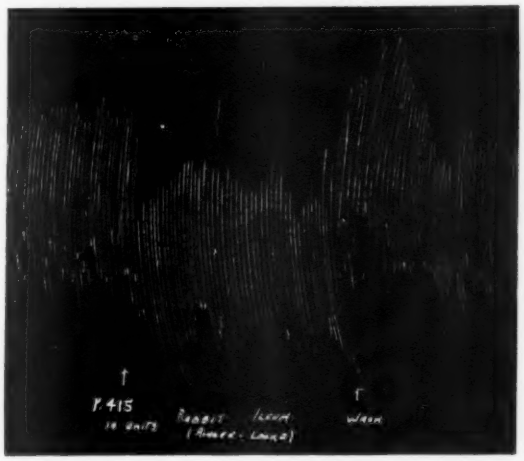

Fig. 3.

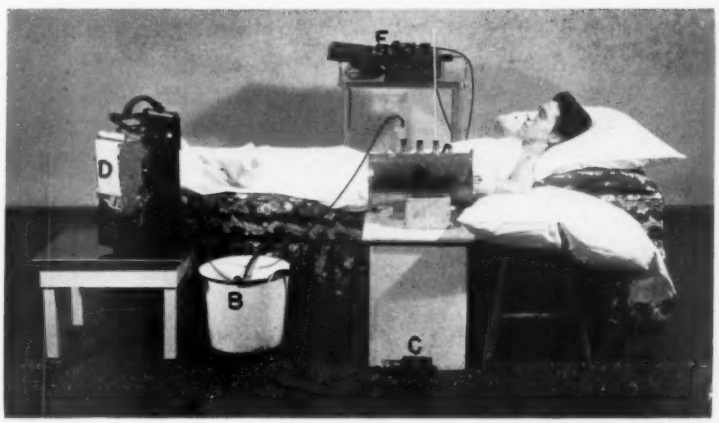

Fig. 4.—*A*, Water jacketed plethysmograph; *B*, constant temperature bath; *C*, circulating pump; *D*, photoelectric recording unit; *E*, potentiometric temperature recording equipment.

APPARATUS FOR STUDIES ON MAN

The plethysmograph (Fig. 4) is a modification of that described by Freeman[14] and by Abramson and his colleagues.[15] It consists of a water-jacketed chamber, open at one end. The open end is sealed with a latex rubber membrane, the central

portion of which is made of the cuff of a surgical rubber glove. The forearm is introduced into the chamber through the rubber cuff, and the hand rests on a specially designed sponge rubber support within the chamber. The cuff of the glove fits snugly about the skin of the forearm at the junction of its middle and distal thirds, forming an air-tight seal. A heavy cardboard gasket, cut to conform to the forearm, is fitted over the outer surface of the membrane. This gasket is kept in place by two shaped sheets of metal which are fastened to the outer aspect of the chamber. Three additional openings into the chamber allow for (1) a rubber hose connection to the recording equipment, (2) a calibrating burette, and (3) a thermometer. Water at 32° C. from a constant temperature bath is circulated through the outer jacket by means of a small, heavy-duty pump.

The recording device, which was described by Martin, Marcellus, and Sykowski,[16] consists essentially of a small rubber diaphragm which transmits volume changes from the chamber to a small mirror, hinged on its longitudinal axis. A beam of light plays on the mirror and is reflected into one of two photosensitive cells. These photosensitive cells, in turn, activate a moving pen which records on a calibrated strip of paper moved by a synchronous motor.

Skin temperature records were made by means of a specially designed chromel-nichron thermocouple* which had an area of 0.25 cm.^{2} and a sensitivity of 0.200 to 0.212 millivolts per degree Fahrenheit, in the temperature range in which we were interested (Fig. 4).

All skin temperatures were taken immediately proximal to the nail bed on the dorsum of the fourth finger. "Cold" responses were elicited by placing the hand in water at 5° C. for a period of thirty seconds.

3. Normal Human Controls.—Sixteen persons were examined. These included ten laboratory workers and six patients who were convalescing from acute infectious diseases. The subject was placed in a comfortable supine position and the forearm adjusted in the plethysmograph. After an interval of thirty minutes, which allowed for the establishment of basal conditions, and during which time the instruments were calibrated, the record was started. Skin temperature readings were taken at periodic intervals throughout the course of the entire experiment.

Normal or spontaneous volume fluctuations, such as those described by Abramson and Katzenstein,[17] caused by spontaneous alterations in the caliber of the venous bed, occurred in a few isolated instances. Usually there were a primary rhythmicity associated with respiratory movements and a superimposed secondary rhythm which showed volume fluctuations of the same order as those observed during the respiratory cycle. The application of the standardized cold stimulus gave rise to an immediate diminution in hand volume; the latter returned to its base level within three minutes after the stimulus was withdrawn. Fig. 6 shows a typical cold-pressor response; the diminution in hand volume of 5 c.c. is indicated by a rise of the writing point, and the subsequent, prompt return of hand volume to its original level is shown by a fall. The intramuscular administration of physiologic saline solution or of

*Six chromel-nichron junctions, arranged in series. This was designed and built for us by the General Engineering Laboratories, General Electric Company, Schenectady, N. Y.

liver extract produced a similar diminution in hand volume in approximately 20 per cent of this normal group. This we attributed to psychogenic factors resulting from the introduction of a hypodermic needle into hypersensitive persons. In the majority of the subjects the administration of the saline or liver extract gave rise to no peripheral volume change. In no instance did the administration of a placebo give rise to an increase in limb volume or any alteration in the intensity of the response to the standard cold stimulus.

The intramuscular administration of 10 units of the active pancreatic extract in 1.0 c.c. of physiologic saline solution rarely elicits any local reaction. Those persons who showed a transient diminution in limb volume after the administration of saline or liver extract usually showed the same diminution after the injection of the active principle. All normal subjects ultimately showed a marked increase in limb volume, associated with an elevation of skin temperature, after the injection of such doses. The maximal effect was reached within fifteen minutes of administration and continued throughout the entire period of observation (ca. two hours). The average volume increase was 12 c.c., and the average temperature elevation, 5° F. More striking than the increase in limb volume was the modification of the response to the cold stimulus. In 68 per cent of this normal group the response to the cold stimulus was entirely abolished, whereas the remainder showed a marked diminution in the intensity and duration of the response. These results are illustrated graphically in Fig. 5, which shows the mean response to the cold stimulus before and after the administration of the active principle.

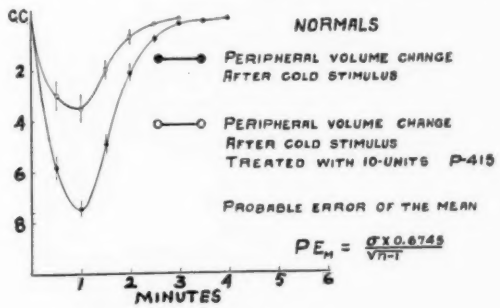

Fig. 5.

4. Peripheral Arterial Disease.—A series of twenty-one patients with established or suspected peripheral arterial disease were examined and treated with the active principle according to the scheme outlined above. These included cases of established Raynaud's disease, Buerger's disease, arteriosclerosis with hypertension, thrombophlebitis, and scleroderma. The majority of those who comprised this group differed from the normal subjects in so far as their response to the standard cold stimulus was concerned. As was pointed out above, the normal persons

required approximately three minutes after the withdrawal of the cold stimulus for the re-establishment of the basal volume level. This group required more than ten minutes for the re-establishment of this level.

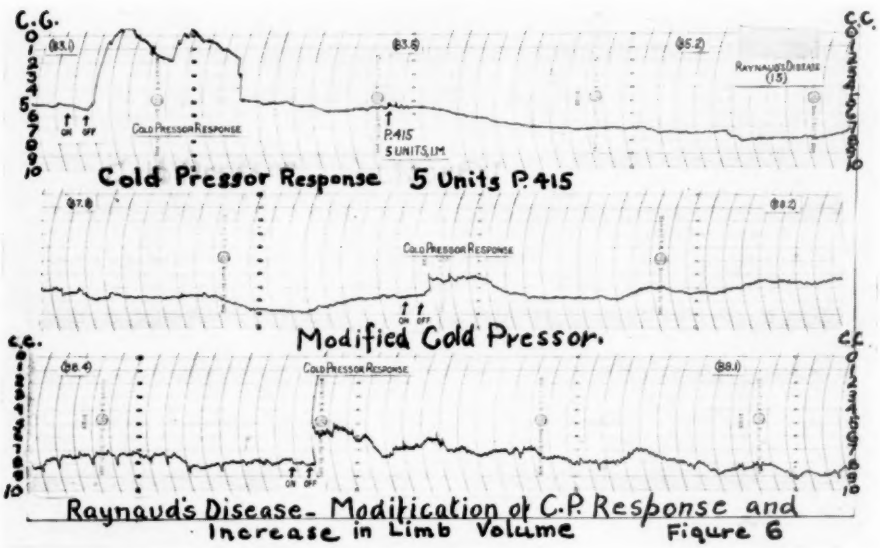

Fig. 6.

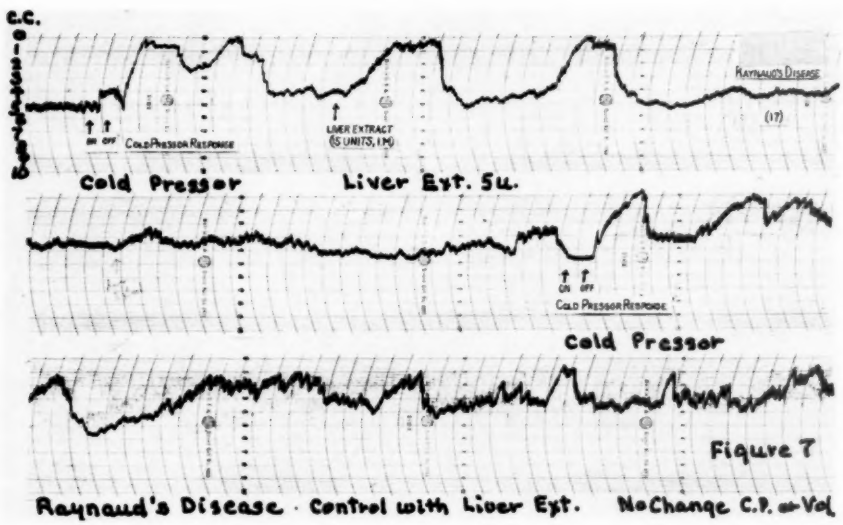

Fig. 7.

Patients suffering from peripheral vascular disease may be divided into two groups: (a) those with a spastic cold-pressor response, and (b) those with a normal response. All of our patients with untreated Raynaud's disease (Fig. 6) fell in the first group. This form of vaso-

spasticity may be encountered also in Buerger's disease, even though the primary lesion is an obliterative angiitis, and it may be an added factor in the symptomatology of the disease. We have not seen the spastic type of response in hypertensive arteriosclerotic patients, but have encountered it in cases of thrombophlebitis and scleroderma. We have also found it in three cases which could not be fitted into any clearly delineated clinical entity, but the patients' clinical manifestations were sufficiently suggestive of peripheral arterial disease to warrant serious consideration of this possibility (Cases 5, 9, 11).

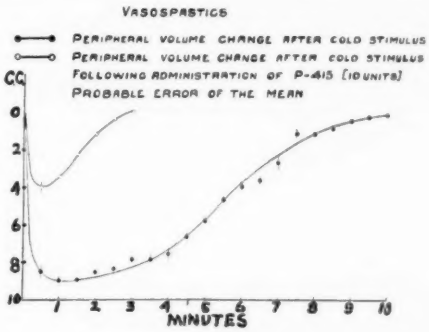

Fig. 8.

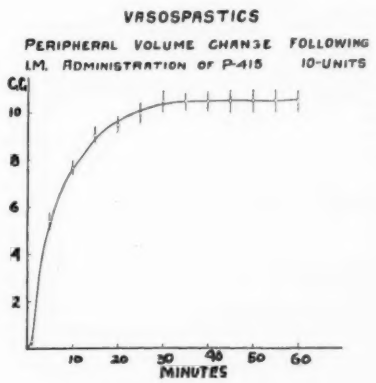

Fig. 9.

The spastic type of response was modified by the administration of 10 units of the active principle, so that it approximated the response of the normal person after medication (Fig. 6). This was associated with an increase in limb volume, elevation of the skin temperature, and, in most instances, symptomatic relief. Such persons, when given a placebo (intramuscular injection of 15 U.S.P. units of liver extract), failed to show any of the changes enumerated above (Fig. 7). The mean values for the cold-pressor response in this group of patients have been ascertained, and are shown in graphic form in Fig. 8. The conversion of this spastic type of volume change to the normal pattern after

the intramuscular administration of 10 units of the active principle is also recorded.

With the exception of the two patients with hypertension and arteriosclerosis and one with Buerger's disease, the entire group showed increased peripheral volume and an elevation of the skin temperature. The maximal effect appeared about fifteen minutes after medication and persisted throughout the entire period of observation. Symptomatic relief lasted from twenty-four to seventy-two hours (Fig. 9).

The details of our observations on a series of patients with peripheral vascular disease are presented.

Case 1.—Miss H. O., aged 30 years. Raynaud's disease.

Thoracic preganglionic (T-2, 3) sympathectomy performed six months prior to examination because of gangrenous changes in the finger tips, followed by improvement.

No vasoconstriction as a result of the application of cold. Ten units of tissue extract produced a slight elevation of skin temperature (2° F.) and slight peripheral vasodilatation (6 c.c.). No peripheral vasodilatation or elevation of skin temperature resulted from the administration of a saline placebo. There has been no return of symptoms. This patient was apparently completely cured by surgical measures.

Case 2.—Mrs. J. M., aged 54 years. Raynaud's disease.

Classical Raynaud's symptom complex which had persisted for fifteen years and had shown marked exacerbation during the preceding two years. Pain of a sharp, lancinating character, in addition to a dull ache.

Spastic response to cold stimulation. Ten units of tissue extract produced a 6° F. elevation of skin temperature and marked (12 c.c.) peripheral vasodilatation. This was associated with immediate symptomatic relief.

Subsequent medication with a saline placebo produced no vasodilatation, no elevation of skin temperature, and no symptomatic relief.

Twenty units of tissue extract produced symptomatic relief for 48 to 72 hours. Patient has been symptom-free for six months.

Case 3.—Miss S. P., aged 18 years. Early Raynaud's disease.

Complained of pain in hands and forearms of three years' duration, brought on by exposure to cold; pain was associated with color changes.

Plethysmographic examination showed spastic reaction to cold stimulation. The administration of 10 units of tissue extract abolished the spastic reaction and was associated with a 4° F. elevation in skin temperature and peripheral vasodilatation (10 c.c.). Complete symptomatic relief.

Subsequent examination showed no change, no vasospasticity, no elevation in skin temperature, and no peripheral vasodilatation after the administration of a placebo (liver extract).

Patient received 10-unit doses of tissue extract at three-day intervals, and this controlled the symptoms. She became free of symptoms with the advent of warmer weather, and treatment was discontinued.

Case 4.—Mrs. A. H. S., aged 64 years. Raynaud's disease.

Characteristic symptom complex, including bilateral pain and color changes in hands and feet after exposure to cold. Symptoms had persisted for twenty-five years and had become markedly worse in the preceding two years.

Plethysmographic examination showed characteristic spastic reaction to cold, which was abolished by the administration of 10 units of tissue extract. This was

associated with a 6° F. elevation in skin temperature and marked peripheral vasodilatation (12 c.c.). There was also complete symptomatic relief which persisted for forty-eight hours.

Subsequent administration of a placebo produced neither subjective nor objective changes.

At the present time the patient receives one dose of 20 units per week, which has maintained symptomatic relief for a period of six months.

Case 5.—Miss J. R., aged 21 years. Early Raynaud's disease (?).

Complained of shooting pain in the right hand, with spread to the shoulder. This was precipitated by exposure to cold and was not associated with color changes.

Plethysmographic examination showed a slight spastic reaction. The administration of 10 units of tissue extract abolished the spastic response, and produced a 6° F. elevation of skin temperature and definite (10 c.c.) peripheral vasodilatation. There was complete subjective relief for a period of twenty-four hours.

Subsequent administration of a placebo produced no objective changes, but was followed by complete symptomatic relief which persisted for approximately twenty-four hours.

Treatment was discontinued.

Case 6.—Miss J. Van A., aged 27 years. Raynaud's disease (?).

Complained of pain in the right hand and forearm, of two years' duration, precipitated by cold. No color changes. Markedly spastic type of response to exposure to cold; the injection of 10 units of tissue extract abolished the spastic response and produced a 6° F. elevation of skin temperature and marked peripheral vasodilatation (12 c.c.). There was partial symptomatic relief.

The administration of a placebo produced no objective changes, but gave symptomatic relief.

Patient was not followed.

Case 7.—Mrs. K. S., aged 40 years. Raynaud's disease.

Classical picture, with pain, color changes, and pregangrenous trophic changes about the finger tips. Pronounced spastic response to cold which was abolished by the administration of 10 units of tissue extract. This was associated with marked peripheral vasodilatation (16 c.c.) and elevation of skin temperature (4° F.). There was complete symptomatic relief for forty-eight hours.

The administration of a placebo produced no objective changes or symptomatic relief.

Six months later the patient was receiving approximately 40 units per week in divided doses and was symptom-free.

Case 8.—Mr. J. B., aged 51 years. Buerger's disease.

Thromboangiitis obliterans demonstrated histologically. Mid-thigh amputation of left leg for gangrenous change of left foot performed eight months earlier. At the same time, the distal phalanges of the fourth and fifth fingers of the left hand and fifth finger of the right hand were amputated.

Patient had a foul-smelling, discharging ulcer on the internal malleolus of the right foot. This was surrounded by a cyanotic, edematous zone, and the edema involved the entire lower third of the leg.

Plethysmographic examination showed a markedly spastic response to cold stimulation; this was abolished by the administration of 10 units of the tissue extract; and, in addition, an elevation of the skin temperature (7° F.), marked peripheral vasodilatation (18 c.c.), and complete relief of symptoms occurred.

The administration of a placebo produced no objective changes and had no influence on the symptoms.

The intramuscular injection of tissue extract at 48-hour intervals (20 units) resulted in complete symptomatic relief and marked improvement in the condition of the ulcer. By the end of the third week the cyanosis and edema had disappeared, and the ulcer presented a clean, granulating surface. No adjuvant therapy was employed in this case, and objective, as well as subjective, improvement occurred without rest in bed.

Case 9.—Mr. J. G., aged 51 years. Buerger's disease (?).

Pain in the left leg of two years' duration. Brawny swelling involving the foot, the ankle, and the lower portion of the leg, with an area of exquisite tenderness over the femoral vein in the inguinal region. The popliteal, posterior tibial, and dorsalis pedis pulses on the left could not be palpated. No history of diabetes, hypertension, or syphilis.

Plethysmographic examination showed a markedly spastic response to cold stimulation which disappeared after the administration of 10 units of the tissue extract. This was associated with a slight (4° F.) elevation of skin temperature and slight (5 c.c.) peripheral vasodilatation. There was no symptomatic relief.

No objective or subjective changes were produced by the administration of a placebo. Patient was not followed.

Case 10.—Mr. J. B., aged 53 years. Buerger's disease.

Symptoms had been present for twenty-four years. During the preceding two years, trophic ulcers developed between the toes of the right foot and did not respond to medication. The popliteal and dorsalis pedis pulses could barely be felt. Exposure to cold produced a typical spastic response which was abolished by the administration of 10 units of tissue extract.

This was associated with a 6° F. elevation of skin temperature, marked peripheral vasodilatation (13 c.c.), and complete symptomatic relief.

No objective or subjective changes occurred after the administration of a placebo.

Six months after the beginning of treatment the patient was symptom-free on 30 to 60 units of tissue extract per week, and the trophic ulcers had disappeared.

Case 11.—Mr. J. O., aged 55 years. Buerger's disease (?).

Patient complained of intermittent claudication of the right leg, with a constant, gnawing pain in both feet, of three years' duration. Twelve years before, after exposure to intense cold, the first and second toes of the right foot were frostbitten, and amputation was performed. There was no history of hypertension or other chronic disease.

The dorsalis pedis and popliteal pulses could not be palpated on the right. He gave a spastic response to cold stimulation which was abolished by the administration of 10 units of tissue extract. This was associated with a slight (3° F.) elevation of skin temperature and slight (7 c.c.) peripheral vasodilatation. There was partial symptomatic relief.

Three weeks after the original examination the patient responded normally to cold stimulation, and the administration of a tissue extract had no significant objective or subjective effect. Subsequently there was progression of the peripheral arterial lesions.

Case 12.—Mr. J. A., aged 35 years. Buerger's disease.

Thromboangiitis obliterans demonstrated histologically. Four weeks prior to examination, mid-thigh amputation was performed because of gangrenous changes in the left foot. The amputation stump was healing poorly, and pain and trophic changes appeared in the other foot.

Plethysmographic examination showed a markedly spastic reaction to cold stimulation which was abolished by the administration of 10 units of tissue extract.

This was associated with a marked (8° F.) elevation of skin temperature, an increase in peripheral volume (16 c.c.), and complete symptomatic relief.

The patient received 10 units of the extract daily during the three-week period of hospitalization, and was free from symptoms. The amputation stump healed rapidly.

Case 13.—Mr. F. M., aged 48 years. Buerger's disease.

Thromboangiitis obliterans demonstrated histologically. Symptoms persisted for three years. Fifteen months before, mid-thigh amputation was performed because of gangrenous changes in the right foot. He complained of intermittent claudication on the left side, the nail beds were cyanotic, and trophic changes were present. The dorsalis pedis pulse could be palpated with difficulty.

Examination showed a normal response to cold stimulation which was not affected by the administration of 10 units of the tissue extract. There were no objective changes.

Subsequently, the administration of 30 units of the tissue extract failed to alter the peripheral circulation or to affect the symptoms.

Case 14.—Mr. M. T., aged 49 years. Buerger's disease.

Intermittent claudication and trophic changes in the left foot for a period of eight months. Both popliteal pulses were palpable, but the dorsalis pedis and posterior tibial on the left were not.

Examination showed a markedly spastic response to cold stimulation which could be abolished by the administration of 10 units of tissue extract. This was associated with an elevation (8° F.) of skin temperature, peripheral vasodilatation (12 c.c.), and symptomatic relief.

Subsequent examination showed neither objective nor subjective changes after the administration of a placebo. The patient was given 40 units of tissue extract per week, which kept him asymptomatic for three weeks, or until the arrival of warm weather.

Case 15.—Mr. J. G., aged 56 years. Arteriosclerosis with claudication.

Complained of a "dead feeling" and pain in both legs for a period of two years. The patient was a diabetic, but the disease was kept under control without insulin.

He gave a spastic response to cold stimulation, which was abolished by the administration of 10 units of tissue extract. This was associated with a 4° F. elevation of skin temperature and slight (6 c.c.) peripheral vasodilatation. The patient remained symptom-free for twenty-four hours.

A placebo produced neither subjective nor objective changes.

The subsequent administration of 10 to 30 units of tissue extract gave varying results; at times symptomatic relief was obtained, and, at other times, there was no effect. Treatment was discontinued.

Case 16.—Mrs. H. W., aged 47 years. Arteriosclerosis, marked hypertension with arteriosclerotic changes, diabetes, and nephrosclerosis.

Complained of pain in both legs on exertion. Normal response to cold stimulation. The administration of 20 units of tissue extract produced no demonstrable effect on symptoms, skin temperature, or limb volume.

Case 17.—Mr. J. B., aged 50 years. Arteriosclerosis, hypertension with marked arteriosclerotic changes.

Complained of pain on exercising and a persistent, nonhealing trophic ulcer on the shin.

Plethysmographic examination showed a normal response to cold stimulation. The administration of 20 units of tissue extract produced no subjective or objective changes.

Case 18.—Mrs. D. Z., aged 66 years. Scleroderma.

Marked scleroderma, verified by biopsy.

Plethysmographic examination showed a markedly spastic response to cold stimulation which was abolished by the intramuscular administration of 10 units of tissue extract; this was associated with slight peripheral dilatation (7 c.c.) and partial symptomatic relief. Skin temperature was not recorded.

Subsequently, the administration of 10 units per day gave the patient considerable symptomatic relief.

Case 19.—Mrs. L. D., aged 69 years. Thrombophlebitis.

Acute thrombophlebitis involving femoral vein. The right leg was swollen, brawny, and exquisitely tender.

There was a markedly spastic response to cold stimulation which was abolished by the administration of 10 units of tissue extract. Slight (6 c.c.) peripheral vasodilatation was associated with questionable symptomatic relief. Skin temperature was not recorded.

Case 20.—Mr. L. P., aged 33 years. Orthopedic disorder (foot strain).

Complained of acute pain in the feet, extending from the soles up to the calves. The pain bore no relation to environmental temperature; it occurred when the patient stood in one place for any length of time. The pain could be relieved by active or passive exercises.

No signs of organic arterial disease. Normal response to cold stimulation. The administration of 10 units of tissue extract produced a slight (2° F.) elevation of skin temperature, slight (8 c.c.) peripheral vasodilatation, and no effect on the symptoms.

Case 21.—Mrs. F. G., aged 37 years. Thrombophlebitis.

Acute thrombophlebitis eighteen months prior to examination. Trophic ulcer on the shin of the left leg. Patient complained of pain on exercise.

Normal response to cold stimulation. The administration of 10 units of tissue extract produced a slight (1° F.) elevation of skin temperature and slight (6 c.c.) peripheral vasodilatation. There was no effect upon the symptoms.

SUMMARY

Table I summarizes the results of treatment with the extract in the twenty-one cases of peripheral arterial disease. It will be noted that there were fifteen instances in which the response to cold was of the spastic type. These patients reacted especially well to the extract; all of them showed significant increases in limb volume and rises in skin temperature. Symptomatic relief was complete in eight cases and partial in four. The three patients in the "spastic group" who failed to benefit symptomatically from administration of the extract had Buerger's disease (Cases 9 and 11) or thrombophlebitis (Case 19). Six patients in the series of twenty-one subjects gave a normal response to cold stimulation, i.e., they showed no evidence of vasospasm. None of these patients received any benefit from injections of the pancreatic extract. In Case 1 the patient's Raynaud's disease was asymptomatic as a result of preganglionic sympathectomy. The operation had evidently completely abolished the abnormal response to cold. Case 13 was one of advanced Buerger's disease, Cases 16 and 17 were examples of arteriosclerosis, Case 20 was one of foot strain with no peripheral vascular disease, and Case 21 was one of thrombophlebitis with ulceration.

TABLE I

CASE	UNTREATED			EFFECT OF TREATMENT WITH P-415 (10 UNITS, I.M.)				
	DIAGNOSIS	COLD NORMAL	STIMULUS SPASTIC	COLD NORMAL	STIMULUS SPASTIC	SKIN TEMP.	VASODILATATION	SYMPTOMS (RELIEF)
1	Raynaud's Dis.	Nil		Nil		+2° F.	+ 6 c.c.	Nil
2	Raynaud's Dis.		+++	x		+6° F.	+12 c.c.	Complete
3	Raynaud's Dis.		++	x		+4° F.	+10 c.c.	Complete
4	Raynaud's Dis.		++++	x		+6° F.	+12 c.c.	Complete
5	Raynaud's Dis. (?)		++	x		+6° F.	+10 c.c.	24 hr. inconstant
6	Raynaud's Dis. (?)		++	x		+6° F.	+12 c.c.	Partial, not followed
7	Raynaud's Dis.		++++	x		+4° F.	+16 c.c.	Complete
8	Buerger's Dis.		++++	x		+7° F.	+18 c.c.	Complete
9	Buerger's Dis. (?)		++	x		+4° F.	+ 5 c.c.	None
10	Buerger's Dis.		++++	x		+6° F.	+13 c.c.	Complete
11	Buerger's Dis. (?)		+	x		+3° F.	+ 7 c.c.	None
12	Buerger's Dis.		++++	x		+8° F.	+16 c.c.	Complete
13	Buerger's Dis.	x		x		+0° F.	+ 0 c.c.	None
14	Buerger's Dis.		+++	x		+8° F.	+12 c.c.	24 hr. complete
15	Arteriosclerosis with Claudication		+++	x		+4° F.	+ 6 c.c.	Partial, inconstant
16	Arteriosclerosis	x		x		No chg.	No chg.	None
17	Arteriosclerosis	x		x		No chg.	No chg.	None
18	Scleroderma		+++	x		Not recorded	+ 7 c.c.	Partial
19	Thrombophlebitis		+++	x		Not recorded	+ 6 c.c.	Questionable
20	Orthopedic Disorder (Foot Strain)	x		x		+2° F.	+ 8 c.c.	None
21	Thrombophlebitis with Ulceration	x		x		+1° F.	+ 6 c.c.	None

CONCLUSIONS

We have presented objective proof of the physiologic activity of a new and protent pancreatic extract. When used on animals and on normal human controls it has been shown to cause peripheral vasodilatation in the limbs, as measured by an increase in volume and a rise in temperature. This extract has a most beneficial symptomatic effect upon nearly all patients with peripheral vascular disease when vasospasm is a prominent feature. Relief has been obtained for periods of one to six months with administration at intervals of two to seven days.

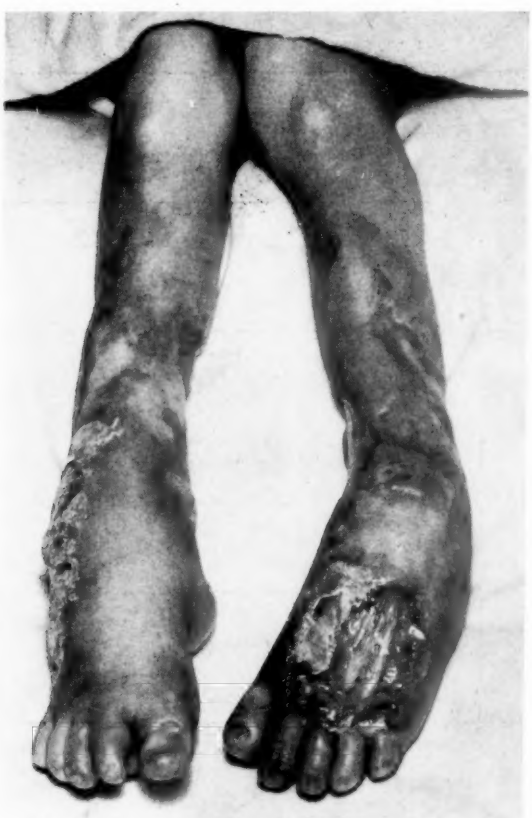

Fig. 10.

ADDENDUM

Since this investigation was completed we have had the opportunity of studying and treating a most unusual patient. Miss G. B., aged 31, hospital number 96038, was admitted to the Albany Hospital May 31, 1942. She gave a history of long-standing Raynaud's disease, with marked ulceration over the feet and ankles, as shown in Fig. 10. Twelve years previously she had a lumbar sympathectomy at another clinic,

with temporary relief of pain for about two years. For the preceding two years she had been bedridden, and dependent on narcotics for relief of pain. With the plethysmographic technique it was found that the patient showed marked vasospasm. The immediate response to tissue extract was feeble, and very little hope of clinical improvement was entertained. However, with doses of 20 units twice a week, plus the use

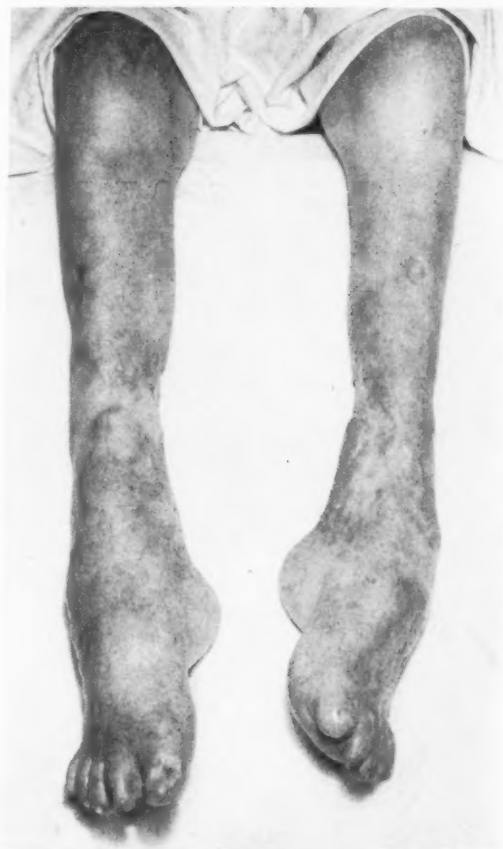

Fig. 11.

of sulfanilamide-sulfathiazole powder, a dramatic response was obtained. The pain had disappeared at the end of two weeks, and healing had begun. By October 17 healing was complete, as shown in Fig. 11.

REFERENCES

1. Frey, E. K., and Kraut, H.: Ein neues Kreislaufhormon und seine Wirkung, Arch. f. exper. Path. u. Pharmakol. **133**: 1, 1928.
2. Gley, P., and Kisthinios, N.: Recherches sur la substance hypotensive du pancréas, Presse méd. **37**: 1279, 1929.
3. Villaret, M., Justin-Besançon, L., and Cachera, A.: Recherches préliminaires sur les substances dites "hypotensives" retirées de certaines insulines, Presse méd. **37**: 633, 1929.

4. Elliot, A. H., and Nuzum, F. R.: The Pharmacologic Properties of an Insulin-Free Extract of Pancreas and the Circulatory Hormone of Frey, J. Pharmacol. & Exper. Therap. **43**: 463, 1931.
5. Wolffe, J. B., Findlay, D., and Dessen, E.: Treatment of Angina Pectoris With a Tissue Vasodilator Extract. (Preliminary Report), Ann. Int. Med. **5**: 625, 1931.
6. Drury, A. N., and Szent-Györgyi, A.: Physiological Activity of Adenine Compounds With Especial Reference to Their Action Upon the Mammalian Heart, J. Physiol. **68**: 213, 1929.
7. Vaquez, H., Giroux, R., and Kisthinios, N.: De l'action de certains extraits pancréatiques dans le traitement de l'angine de poitrine, Presse méd. **37**: 1277, 1929.
8. Wolffe, J. B.: Angina Pectoris. Its Treatment With Insulin-Free Pancreatic Extract. Tissue Extract No. 568, Delaware State M. J. **7**: 123, 1935.
9. Wolffe, J. B., and Digilio, V. A.: Pancreatic Extract (Tissue Extract No. 568); Its Use in Treatment of Hypertension, J. Lab. & Clin. Med. **22**: 374, 1937.
10. Fisher, M. M., Duryee, A. W., and Wright, I. S.: Deproteinated Pancreatic Extract (Depropanex). Effect in the Treatment of Intermittent Claudication Due to Arteriosclerosis Obliterans, AM. HEART J. **18**: 425, 1939.
11. Lesuk, A.: To be published.
12. Werle, E., and Urhahn, K.: Ueber den Aktivitätszustand des Kallikreins in der Bauchspeicheldrüse, Biochem. Ztschr. **304**: 387, 1940.
13. Greene, Charles W.: Dilation of the Coronary Vessels by Certain Organic Extracts and Drugs, J. Pharmacol. & Exper. Therap. **57**: 98, 1936.
14. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, Am. J. Physiol. **113**: 384, 1935.
15. Abramson, D. I., Zazeela, H., and Marrus, J.: Plethysmographic Studies of Peripheral Blood Flow in Man. Physiologic Factors Affecting Resting Blood Flow in the Extremities, AM. HEART J. **17**: 206, 1939.
16. Martin, S. J., Marcellus, F. S., and Sykowski, P.: Plethysmographic Studies With Special Reference to Waves of Respiration, J. Lab. & Clin. Med. **24**: 111, 1938.
17. Abramson, D. I., and Katzenstein, K. H.: Spontaneous Volume Changes in the Extremities, AM. HEART J. **21**: 191, 1941.

PERICARDIAL EFFUSION IN MYXEDEMA

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EFFUSION into the pericardium and other serous cavities is a complication of myxedema on which few data are available. Zondek[1] first described myxedema heart disease as a clinical entity, and Gordon[2] first proved that pericardial effusion might account for at least part of the apparent cardiac enlargement. The occurrence of serous effusions was noted at autopsy in cases of myxedema as early as 1888.[3] Tatum[4] and Goldberg[5] reproduced pericardial effusion in thyroidectomized sheep and goats. Freeman[6] reported the first thoroughly described case of massive pericardial effusion in myxedema. Since his report, other instances have been recorded.[7, 8] Although the case described by Merrill[9] resembled myxedema clinically, the basal metabolic rate was elevated. In the case reported by Carns and Lee,[10] the presence of pericardial fluid was not demonstrated by aspiration. Two patients with untreated myxedema who came to autopsy at the Massachusetts General Hospital had pericardial effusion, although one was small in amount.[11] Often the picture is complicated by the development of arteriosclerosis, especially in the coronary arteries, if the myxedema remains untreated for a period of years.

The following two cases, in both of which there was underlying arteriosclerotic heart disease, add a few data, including the first quantitative studies on the cholesterol content of the pericardial fluid, and are interesting because of the variation in response to the administration of thyroid substance.

CASE 1.—A 53-year-old, white, farm housewife, was admitted to Duke Hospital October 1, 1938, complaining of weakness, intermittent swelling of the abdomen, and slight dyspnea, of eighteen months' duration. The feet were always cold.

The patient was pale, undernourished, breathing quietly, and not orthopneic. Speech was slow and the voice was hoarse. The tongue showed no papillary atrophy. The skin was dry and thickened. The breath sounds at the bases of the lungs were distant. The heart was enlarged, the precordium quiet, the rate slow, and the sounds distant; the blood pressure was 120/80. The abdomen was rounded, shifting dullness was present, and the liver extended 8 cm. below the costal margin. Pitting edema was present over the sacrum, but not over the legs.

The hemoglobin was 10.9 Gm., the erythrocytes numbered 2,600,000, the color index was 1.3, and the mean corpuscular volume was 140 cubic micra. The urine contained no albumin. Gastric analysis showed 64 degrees of free HCl after the injection of histamine. The total serum protein was 6.4 per cent, with albumin 3.6 per cent, and globulin 2.8 per cent; the cholesterol was 330 mg. per cent. The basal metabolic

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rate was minus 31 per cent. The oral glucose tolerance test revealed a flat curve. Fluoroscopic examination indicated pericardial and bilateral pleural effusion (Fig. 1).

On the fourth hospital day, fluid was removed from the peritoneal and pleural cavities for diagnosis; 125 c.c. were removed from the pericardium, and 25 c.c. of air were injected. After this the venous pressure fell from 300 to 135 mm. of water, the electrocardiogram showed an increase in voltage, and the blood pressure rose to 130/80, but no subjective improvement was noted. After one day on 64 mg. of desiccated thyroid gland, without diuretics or digitalis, a dramatic diuresis began, reaching a peak of 2,300 c.c. after four days of treatment with the same dose; the free fluid soon disappeared from the serous cavities. The total protein content of the pericardial fluid was 4.9 per cent, of the pleural fluid, 2.9 per cent, and of the peritoneal fluid, 2.4 per cent.

The patient took desiccated thyroid irregularly until April, 1941, when nicotinic acid tablets were substituted. She was readmitted May 14, 1941, at which time she

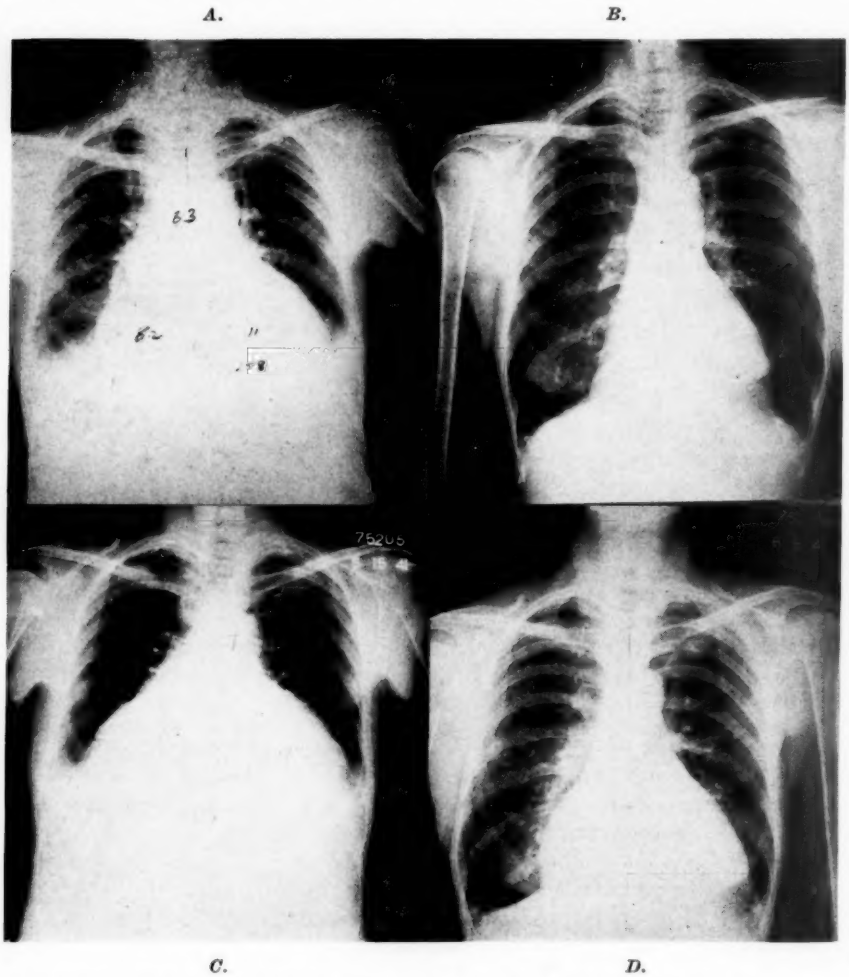


Fig. 1.—Case 1. *A*, Massive pericardial and small pleural effusion, before therapy. *B*, Complete disappearance of effusions on thyroid therapy alone. *C*, Recurrence of effusions after withdrawal of thyroid. *D*, Improvement a second time on thyroid therapy, after failure to improve on digitalis.

was orthopneic, and had physical and roentgenologic evidence of fluid in all the serous cavities (Fig. 2), peripheral edema, and signs of myxedema. The hemoglobin was 13 Gm., the erythrocytes numbered 4,400,000, the color index was 0.95, the mean corpuscular volume, 97.7 cubic micra, the basal metabolic rate, minus 35 per cent, the vital capacity, 600 c.c., the venous pressure, 190 mm. of water, and the serum cholesterol, 270 mg. per cent; the serum proteins were 5.0 per cent, with albumin 2.7 per cent and globulin 2.3 per cent, and the circulation time was 19 seconds by the calcium gluconate method. The urine contained no albumin. The pericardial fluid contained 4.3 per cent of total protein and 92 mg. per cent of cholesterol.

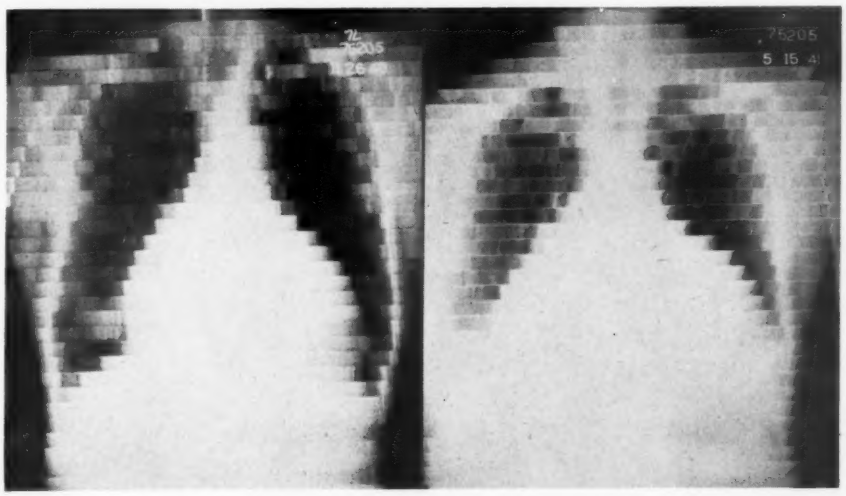


Fig. 2.—Case 1. *A*, Roentgenkymograph when patient was on irregular doses of thyroid, showing absence of pulsations over the lower third of the heart and good pulsations over the great vessels, indicating recurrence of small pericardial effusion without impairment of ventricular contraction. *B*, Recurrence of massive pericardial and small pleural effusion after complete withdrawal of thyroid therapy; the small pulsations over the great vessels indicate feeble ventricular contractions.

After rest in bed, restriction of fluids, and complete digitalization produced no response, 64 mg. of thyroid substance were administered daily, with a marked diuresis of 2,700 c.c. on the second day and a weight loss of 3 kg. in two days. On the eleventh and sixteenth days the thyroid dosage was increased, with the result that there was a second and third diuresis, each lasting three days. The edema, serous effusions, mental sluggishness, and coolness and thickening of the skin disappeared.

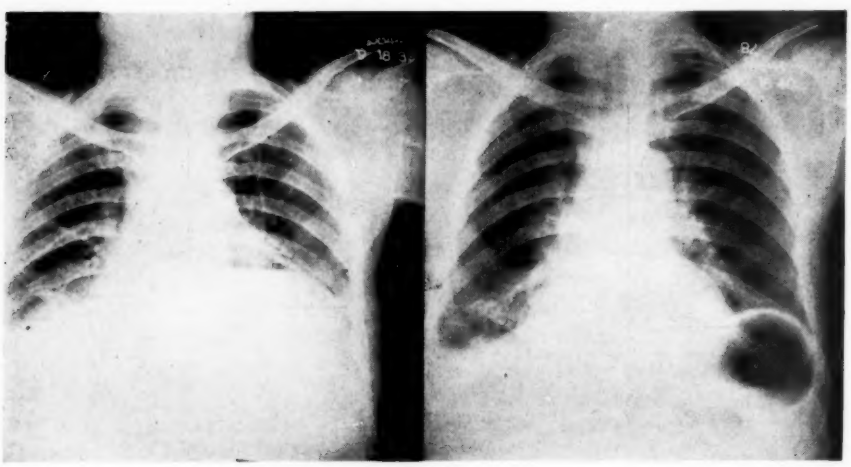
CASE 2.—A 62-year-old white farmer was admitted to the Duke Hospital September 11, 1939, complaining of orthopnea and edema of one month's duration. He had been seen in 1932, 1934, and 1937, when he had pellagra, anemia, and hypothyroidism, and had always responded promptly to therapy with desiccated thyroid, iron, and yeast.

The patient presented the classic appearance of myxedema. Signs of fluid were present at the bases of both lungs. The supracardiac dullness was greatly increased (Fig. 3), and the heart sounds were barely audible; the blood pressure was 168/114. The abdomen was distended and tympanitic, and the liver was enlarged. Pitting edema was present below the knees. The skin over the hands and feet was rough, dry, red, and scaling.

The hemoglobin was 9 Gm., the erythrocytes numbered 3,100,000, the basal metabolic rate was minus 39 per cent, the serum proteins were 6.4 per cent, with

albumin 3.3 per cent and globulin 3.1 per cent, and the cholesterol was 155 mg. per cent. The urine contained a small amount (1+) of albumin. Fluid aspirated from the pericardium contained 5.7 per cent of protein, but also 9,000 erythrocytes per c.mm., probably as the result of trauma. After receiving 100 mg. of thiamin chloride daily, intravenously, for four days without diuresis, the administration of thyroid substance was started, but the expected improvement did not occur. After subsequent digitalization, the edema and pleural and pericardial effusion disappeared, but some evidence of ascites remained.

At home he discontinued medication, and returned in October, 1940, with classic myxedema, but with serous effusion only in the right pleural sac. The skin lesions of pellagra had recurred.



A. *B.*

Fig. 3.—Case 2. *A*, Pericardial effusion after partial aspiration of fluid and replacement with air, before thyroid administration and after failure of vitamin therapy. *B*, Small recurrent pleural effusion on right after thyroid therapy was discontinued, and clinical signs of myxedema had returned.

The hemoglobin was 9.5 Gm., the erythrocytes numbered 2,450,000, the color index was 1.2, the mean corpuscular volume, 98 cubic micra, and the basal metabolic rate, minus 34 per cent. The urine contained no albumin.

The pellagra responded promptly to nicotinic acid, and the myxedema, to thyroid substance. He received no digitalis.

DISCUSSION

Of these two instances of pericardial effusion in association with myxedema, the first was undoubtedly caused by the myxedema itself, for the fluid disappeared under thyroid replacement therapy, recurred after complete withdrawal of thyroid, did not disappear under digitalis therapy, and did respond a second time to thyroid administration. The effusion in the second case did not respond to thyroid substance alone, but also required digitalis, and did not recur on withdrawal of thyroid and digitalis. In each of these cases there was evidence of underlying arteriosclerotic heart disease. The more severely damaged heart (Case 2) did not respond to thyroid substance alone, and the second response in

TABLE I

AGE	SEX	DURATION	B. M. R. %	URINE ALBUMIN	BLOOD				PERICARDIAL FLUID								
					TOTAL PROTEIN %	ALB. %	GLOB. %	CHOLES. MG. %	CULTURE	G.P.*	W.B.C.	PMN %	LYMPH. %	MON. %	SP. GR.	TOTAL PROT. %	CHOLES. MG. %
68[2]	M		-42							Neg.							
39[6]	M	6 yr.	-45	Trace					Neg.	Neg.		50	12	38	1.019	4.5	
54[9]	F	3 yr.	+19	Trace				278	Contaminated	Neg.	75		100		1.020		Crystals
48[7]	F	10 yr.		Neg.	6.4	3.8	2.6		Neg.	Neg.	400		99		1.022	5.0	
		15 yr.	-50					357	Neg.	Neg.	2600		99		1.020	3.2	
[8]	F	3 yr.	-45	Trace				236	Neg.								
54[10]	F	3 mo.	-28	Neg.				227									
53	F	1½ yr.	-31	Neg.	6.4	3.6	2.8	319	Neg.		72		100		1.015	4.9	92
		4 yr.	-35	Neg.	5.0	2.7	2.3	270			109	56	34	10		4.3	
62	M	7 yr.	-39	1+	6.4	3.3	3.1	155	Neg.						1.020	5.7	
		8 yr.	-34	Neg.	6.5	2.4	4.1	292									

*Guinea pig inoculation.

the case of the less severely damaged heart (Case 1) was not so dramatic as the first. The amount of thyroid required to produce diuresis was small, which has been noted before. The possibility of beriberi heart disease in the second case was ruled out by a trial on adequate doses of thiamin; although no unquestioned instance of beriberi heart disease has ever been recognized in this clinic, the simultaneous occurrence of another vitamin deficiency state—pellagra—which is a rare happening, according to Greene,[12] made this conceivable.

Other interesting features presented by these cases, and probably related to associated deficiency states, were the hyperchromic, macrocytic anemia, with free gastric HCl after histamine stimulation, and the low glucose tolerance curve which quickly became normal with thyroid therapy. Delayed relaxation of the tendon reflexes, first observed in myxedema by Chaney, was observed.[13]

The cholesterol content of the pericardial fluid was very much less than that recorded in a case of tuberculous "cholesterol pericarditis."[14] No data on this point could be found in other cases of myxedema. In our case the level was much lower than that of the blood. The protein content of the fluid was similar to that observed by others, and was uniformly less than that of the blood serum. No explanation has ever been offered for the presence of leucocytes, often polymorphonuclears, in the pericardial fluid. The fluids have been sterile on culture and guinea pig inoculation, except in the case of Merrill,[9] in which contamination was suspected.

The absence of more than a trace of albumin in the urine would indicate that, if cardiac failure, *per se*, were responsible for the effusion, it was of such minor degree that renal engorgement was not present; this might be a helpful differential point.

The electrocardiograms showed an increase in voltage after the administration of thyroid substance; no changes were noted which would indicate the presence or absence of pericardial fluid.

The roentgenkymograms in Case 1 (Fig. 2) showed absence of pulsations over the lower third of the heart, with good pulsations over the great vessels; they indicated no impairment of ventricular contraction, even though pericardial effusion was developing after incomplete withdrawal of thyroid therapy. The pulsations over the great vessels were greatly reduced after complete withdrawal of thyroid therapy and the development of massive pericardial effusion. Study of additional cases of myxedema heart by means of the roentgenkymograph, and perhaps other methods, may produce evidence that muscular relaxation is impaired in the ventricle as well as in skeletal muscle.

SUMMARY

Pericardial effusion is a rare complication of myxedema heart disease. The factors responsible are unknown, but myocardial failure is thought to be a minor one. The laboratory data in cases of pericardial effusion

associated with myxedema have been tabulated. The protein and cholesterol contents of the pericardial fluid are less than those of the blood. No adequate explanation has been offered for the occasional presence of leucocytes, especially polymorphonuclear leucocytes, in the fluid.

REFERENCES

1. Zondek, H.: Das Myxöedemherz, München. med. Wchnschr. **65**: 1180, 1918.
2. Gordon, A. H.: Some Clinical Aspects of Hypothyroidism, Canad. M. A. J. **20**: 8, 1929.
3. Report of a Committee of the Clinical Society of London, Nominated December 19, 1883, to Investigate the Subject of Myxedema, Tr. Clin. Soc. Lond. Supp. V. 21, 1888.
4. Tatum, A. L.: Studies in Experimental Cretinism, With Suggestions as to a Biological Test for Thyroid Secretion, Proc. Am. Physiol. Soc., 1912-13, Boston, p. 23.
5. Goldberg, S. A.: Changes in Organs of Thyroidectomized Sheep and Goats, Quart. J. Exper. Physiol. **17**: 15, 1927.
6. Freeman, E. B.: Chronic Pericardial Effusion in Myxedema: Report of Case, Ann. Int. Med. **7**: 1070, 1934.
7. Marzullo, E. R., and Franco, S.: Myxedema With Multiple Serous Effusions and Cardiac Involvement (Myxedema Heart), AM. HEART J. **17**: 368, 1939.
8. Feasby, W. R.: Pericardial Effusion in Myxedema. Report of a Case in Which Intrapericardial Pressure Was Measured, AM. HEART J. **19**: 749, 1940.
9. Merrill, A. J.: Cholesterol Pericarditis, AM. HEART J. **16**: 505, 1938.
10. Carns, M. L., and Lee, H. J.: Pericardial Effusion in Myxedema; Report of Case, Wisconsin M. J. **35**: 33, 1936.
11. Lerman, J., Clark, R. J., and Means, J. H.: The Heart in Myxedema. Electrocardiograms and Roentgen-Ray Measurements Before and After Therapy, Ann. Int. Med. **6**: 1251, 1933.
12. Greene, J. A.: The Coexistence of Myxedema and Pellagra in the Same Patient, Am. J. M. Sc. **195**: 618, 1938.
13. Chaney, W. C.: Tendon Reflexes in Myxedema: A Valuable Aid in Diagnosis, J. A. M. A. **82**: 2013, 1924.
14. Daniel, G., and Puder, S.: Perikarditis et Pleuritis Cholesterinea, Virchows Arch. f. path. Anat. **284**: 853, 1932.

AORTIC ANEURYSM WITH RUPTURE INTO THE PULMONARY ARTERY

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ANEURYSMS of the aorta are not uncommon, especially in communities with a large Negro population. Rupture of such an aneurysm into the pulmonary artery, however, is sufficiently unusual and interesting to warrant special attention. It is of further interest that such a rupture is compatible with life for a varying period of time, and, in some instances, as in one of our cases, can be diagnosed ante mortem when there is a peculiar, continuous, "humming-top" murmur. Probably the most recent case report of this disease is that of White, Chamberlain, and Kelson.[1] These authors state that there were about fifty cases on record before 1913, and that there have been about a dozen reports in the last twenty-five years. The survival period in the cases reviewed by these authors ranged from a few hours to four years. Thurman,[2] Peacock,[3] Taylor,[4] and Kappis[5] were among the early writers and investigators in this field.

CASE REPORTS

CASE 1.—The patient was a 40-year-old colored woman who came to the hospital July 27, 1941, complaining of palpitation, weakness, swelling of the ankles, and abdominal pain. These complaints began two and one-half months previously. There was also intermittent precordial pain, radiating to the left flank. During the two months previous to admission she complained of attacks of loss of consciousness three or four times daily; these were brought on by exertion, and lasted for approximately fifteen minutes. Vomiting had also been troublesome for a month before admission.

There was no past history suggestive of a primary syphilitic lesion or of antisyphilitic treatment.

On admission, the patient's temperature was 98.6°, the pulse rate, 80, the respiratory rate, 20, and the blood pressure, 144/40. Physical examination showed obvious respiratory difficulty, pallor of the conjunctivae, and distention of the neck veins. The trachea was in the midline, and no tracheal tug was noted; râles were heard at the bases of both lungs. The heart was enlarged to the sixth intercostal space in the anterior axillary line on the left. A thrill was felt in the second and third intercostal spaces to the left of the sternum. In the pulmonic area and above, a loud, harsh systolic murmur, with a long, low diastolic murmur, was heard. These murmurs together suggested the more or less classical continuous "humming-top" murmur. The pulmonic second sound was somewhat accentuated;

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the pulmonic first sound was obscured by the murmur. There was no detectable increase in the width of sternal dullness at the base of the heart. The liver was palpable on the right below the level of the umbilicus. Fluid was thought to be present in the abdomen. The reflexes were equal and active. There was edema of the feet, legs, and over the sacrum.

The blood cell count was normal. Urinalyses showed a specific gravity which varied between 1.014 and 1.025, and albumin, erythrocytes, leucocytes, and casts. Both the Kline and Kolmer reactions on the blood serum were strongly positive on two occasions. The blood urea varied between 21 and 44.1 mg. per cent. The blood glucose and protein were within normal limits. A phenolsulfonephthalein test of kidney function on Sept. 23, 1941, showed an excretion of only 35 per cent of the dye in two hours. A roentgenogram of the chest on July 27, 1941, showed enlargement of the cardiac shadow and evidence of an aneurysm of the arch of the aorta. On Aug. 8, 1941, diotrast was given intravenously and radiograms taken. The latter showed what appeared to be enlargement of the pulmonary artery. Electrocardiograms indicated the presence of myocardial disease. A cardiac sound tracing on Aug. 7, 1941, showed a systolic murmur which was loudest at the base, and also a diastolic diminuendo murmur at the base. Several fluoroscopic examinations gave evidence of enlargement of the right and left ventricles, with prominence of the aortic knob and pulmonary artery.

The patient was afebrile on admission and remained so throughout her period in the hospital, except for occasional transient rises to 100° F. Dyspnea and edema continued. The venous pressure was elevated. Vomiting was troublesome. The râles in the lungs became more marked, dyspnea and edema became more pronounced, and the patient died on Oct. 27, 1941.

At necropsy, edema was present over the feet, legs, hands, and sacrum. The right pupil was slightly larger than the left. The edge of the liver was palpable 9 cm. below the right costal margin. There were about 600 c.c. of clear yellow fluid in the peritoneal cavity, 200 to 300 c.c. in each pleural cavity, and about 100 c.c. of slightly cloudy fluid in the pericardial cavity. The heart was markedly enlarged and weighed approximately 550 Gm. The right auricle was dilated, and the right ventricle showed marked hypertrophy; its wall measured 9 mm. in thickness. The pulmonary artery and its right branch were markedly dilated. The left pulmonary artery appeared relatively small. On opening the heart and great vessels, it was noted that when a probe was passed through the pulmonarly artery it extended into the aorta. The first part of the aorta was not enlarged. Just beyond the origin of the left subclavian artery, however, there was a large, saccular dilatation of the aorta (Fig. 1*A*). This sac extended downward and slightly to the left. On looking into the sac, the probe passed from the left pulmonary artery was seen to be protruding into the sac through an elliptical opening which measured 6 mm. in length. The edges of this opening appeared rather smooth (Fig. 1*B*). The sac measured 5 cm. in diameter. Its wall was inelastic. Its inner surface was wrinkled and firm, with some roughening. The external surface was firmly bound down by fibrous tissue to the surface of the left pulmonary artery. In the first part of the aorta, some pink elevated plaques were seen. There was longitudinal wrinkling of the intima which suggested syphilis. No valvular lesions were seen. There were no definite widening of the commissures of the aortic valve cusps and no narrowing of the coronary ostia. The left ventricular wall measured 1.5 cm. in thickness.

The right lung was larger and much firmer than the left. The external surface of the right lung was brown and mottled. Its cut surface was brown and firm. The left lung was more crepitant, and gray in color. The spleen weighed 125 Gm. and presented several small, wedge-shaped areas of infarction. The liver weighed 1,025 Gm. and showed gross evidence of congestion and fatty degeneration.

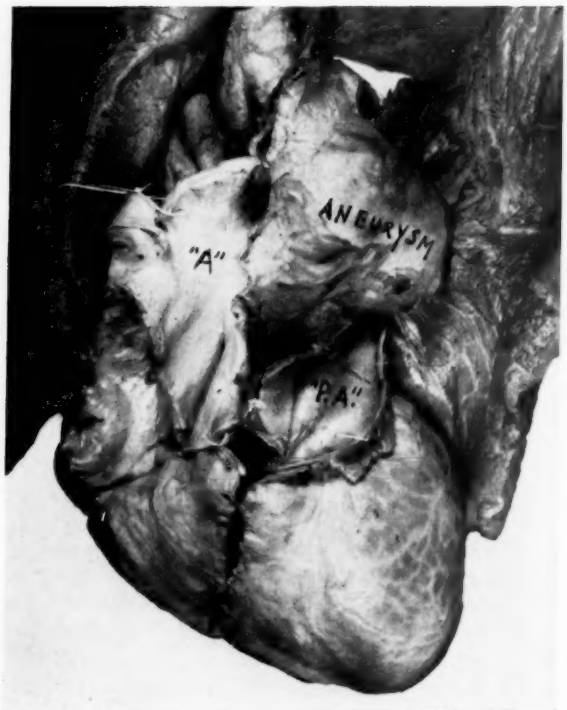

Fig. 1A.—Case 1. Ascending portion of aorta shown opened at "A." Aneurysm lies in transverse portion of arch of aorta and communicates with left branch of pulmonary artery. Pulmonary artery is shown opened at "P.A."

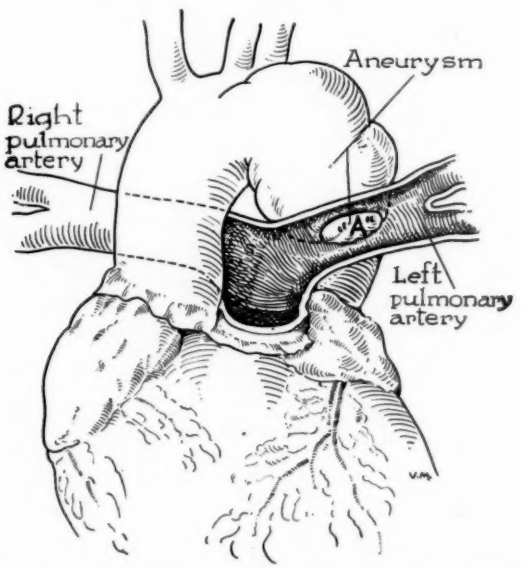

Fig. 1B.—Case 1. Diagrammatic representation, showing location of aneurysm, compression of left branch of pulmonary artery, and rupture into this vessel at "A."

Microscopically, there was marked thickening of the alveolar walls of the right lung, and an increased amount of fibrous tissue and congestion of capillaries were noted. Many of the alveoli contained "heart failure" cells. There was thickening of the vessel walls throughout.

Sections of the heart showed some endocardial thickening, and fragmentation and hypertrophy of myocardial fibrils.

In the aortic wall, well-defined focal accumulations of lymphocytes were noted in the outer media and adventitia. The lymphocytes were most numerous in the region surrounding the small vasa vasorum. There was intimal proliferation, with narrowing and stenosis of the lumina of these small vessels (Fig. 2).

Pathologic Diagnoses.—(1) Hypertrophy and dilatation of the heart, (2) saccular aneurysm of the distal part of the transverse portion of the arch of the aorta, with erosion into the left pulmonary artery, (3) chronic congestion of lungs, liver, spleen, and kidneys, (4) infarction of spleen, and (5) syphilitic aortitis.

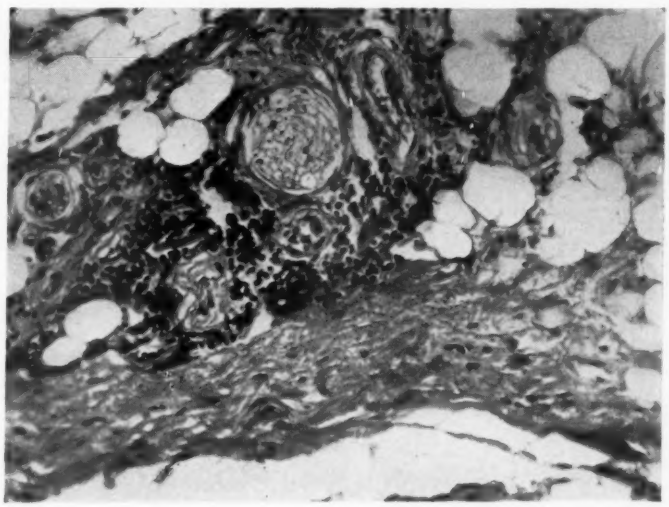

Fig. 2.—Section of wall of aorta, showing endarteritis and perivascular round cell accumulations about the vasa vasorum.

CASE 2.—The patient was a 40-year-old colored man who was admitted to Charity Hospital Jan. 2, 1942, with the history of having been perfectly well until three months previously, when he developed a slight, nonproductive cough. Five days prior to admission he noticed a "snap in his chest" which was associated with pain in the left shoulder and marked dyspnea. The dyspnea became increasingly severe. Cough persisted until the day before admission to the hospital, when the sputum was frothy and bloodtinged.

He had lost 18 pounds in the preceding month. He gave a history of having had a "chancre" ten years before, after which he received several "injections into the hip" over a period of one month.

On admission, the blood pressure was 120/70, the temperature, 99° F., and the pulse rate, 100. He was markedly dyspneic and showed slight cyanosis of the mucous membranes. The trachea was in the midline. Fine râles were scattered diffusely over both lungs. The heart was not enlarged to percussion. A loud "buzzing" sound, extending through systole and diastole, was heard over the pulmonic area. The aortic sounds were absent. A thrill, extending through systole and diastole, was felt in the pulmonic area. The liver was palpable at the costal margin.

Fig. 3*A*.—Case 2. Dotted lines at *A* represent opening into saccular aneurysm, viewed from aortic side. Aneurysm and clot contained therein are shown at *B*. *C* represents border where wall of aorta and pulmonary artery have been eroded and destroyed, with rupture into the latter vessel at its bifurcation. *D* shows markedly dilated opening of right pulmonary artery.

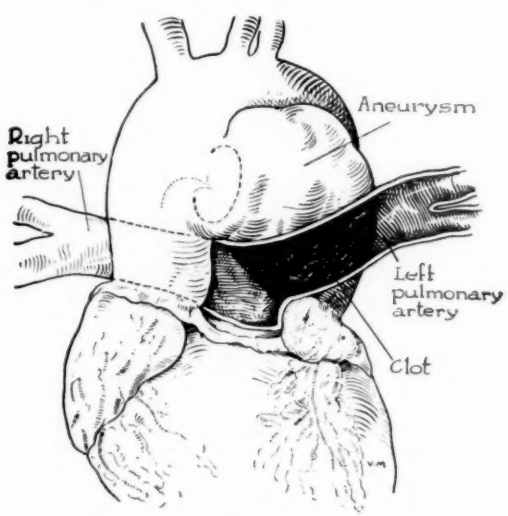

Fig. 3*B*.—Case 2. Diagrammatic representation, showing location of aneurysm in ascending portion of aortic arch, with compression and destruction of wall of left pulmonary artery. Rupture occurred into pulmonary artery at its bifurcation at border of the laminated clot in the aneurysm.

Laboratory examination showed slowing of the circulation time and increased venous pressure. An electrocardiogram revealed no evidence of myocardial disease. A roentgenogram of the chest showed widening of the mediastinal shadow at the base of the heart and just above this area.

The patient failed to respond to all therapeutic measures. He died Jan. 3, 1942, about fifteen hours after coming to the hospital.

Clinical Diagnosis.—Aneurysm of the aorta, with rupture into the pulmonary artery.

At necropsy, a small amount of free fluid was found in the peritoneal and pleural cavities. The heart was not particularly enlarged. There was a slight degree of hypertrophy of the walls of the ventricles. The chambers of the heart, especially the right auricle and ventricle, showed considerable dilatation. The endocardial surface was smooth and glistening. The valve cusps were not thickened. The ostia of the coronary arteries were normally patent.

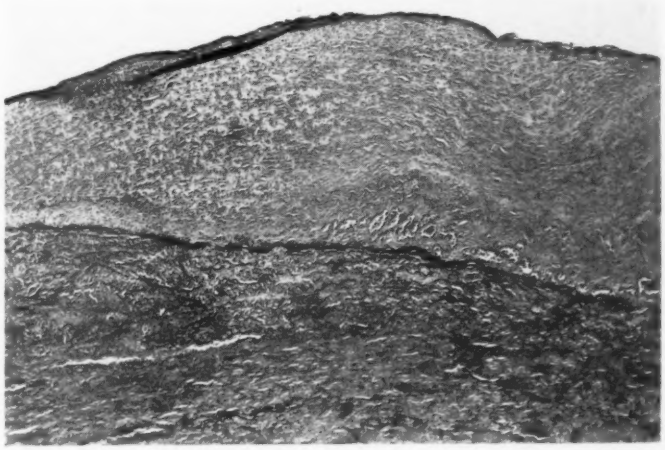

Fig. 4.—Section of wall of aorta. Upper half, showing marked thickening and proliferation of intimal structures.

On external examination of the thoracic aorta, a rather marked saccular dilatation of the ascending portion, about 3 cm. above the aortic valve, was found. This sac was pressing against the pulmonary artery. On opening both of these vessels, freshly clotted blood was seen to extend continuously from the aorta into the pulmonary artery through an opening at the margin of a lamellated clot. This lamellated clot measured 5 cm. in diameter and practically filled the depths of the saccular dilatation of the aorta, except for the area of communication into the pulmonary artery. On further examination, it was seen that the walls of both the aorta and the pulmonary artery had been completely destroyed at the site of the sac, and that the lamellated clot formed the only barrier between the two vessels over an area which measured 5 cm. in diameter (Fig. 3*A*). Thus, although the actual communication between the two vessels appeared to be relatively small (1 to 2 cm.), their walls were destroyed over a considerable area, making a potential communication 5 cm. in diameter. The right branch of the pulmonary artery was readily seen below and behind the site of the aneurysm. The left branch of the pulmonary artery appeared to be completely occluded at its origin by pressure of the sac (Fig. 3*B*). Its orifice was therefore located with difficulty. The lungs showed evidence of chronic passive congestion; this was possibly slightly more pronounced in the right lung than the left.

The intimal surface of the aorta showed the typical "tree-bark" wrinkling and thickening of syphilitic mesaortitis. There were also elevated pink areas and gray glistening plaques. The pulmonary artery and its right branch were markedly dilated.

Microscopically, the aortic wall showed perivascular lymphocytic infiltration and intimal proliferation of the vasa vasorum. There were also markedly hyperplastic areas of the intima of the aorta itself (Fig. 4). The Weigert stain showed disruption and destruction of the normal elastic fibrils, with replacement by fibrous tissue (Fig. 5).

Pathologic Diagnoses.—(1) Aneurysm of the ascending aorta, with rupture into the pulmonary artery, and (2) syphilitic aortitis.

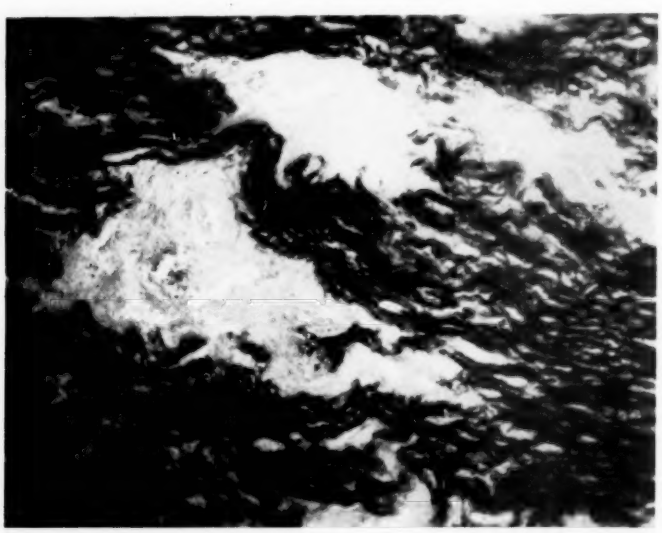

Fig. 5.—Weigert stain of section of aorta, showing disruption and destruction of normal histologic structures, especially elastic fibrils, with fibrous tissue replacement.

DISCUSSION

In a study of 1,197 cases of ruptured aneurysm of the thoracic aorta, Boyd[6] found that in 3.7 per cent the rupture occurred into the pulmonary artery. This is in accord with Lemann's[7] series of 529 ruptures of thoracic aortic aneurysms, in 18, or 3.0 per cent, of which the rupture occurred into the pulmonary artery. In only one of Potter's[8] 46 cases and one of Kampmeier's[9] 98 cases of ruptured thoracic aneurysms did rupture occur into the pulmonary artery. Woolley[10] reported a series of 6 ruptured aneurysms of the arch of the aorta, of which one involved the pulmonary artery.

Kampmeier's[9] study included a group of 1,038 cases in which the diagnosis of aneurysm of the thoracic aorta was made at the Charity Hospital in New Orleans between 1905 and 1935. In none of these did rupture take place into the pulmonary artery.

Since Jan. 1, 1935, through April 15, 1942, the following statistics have been compiled from the records of patients at the Charity Hospital:

Aneurysm of thoracic aorta (autopsy diagnosis)		121
Aneurysm of thoracic aorta (clinical diagnosis; no autopsy done)		336
Total		457
Rupture of aneurysm of thoracic aorta (autopsy diagnosis)		18
Rupture of aneurysm of thoracic aorta (clinical diagnosis; no autopsy done)		12
Total		30
Sites of rupture (autopsy diagnosis):		
Pulmonary artery	2	
Great veins	4	
Trachea	6	
Esophagus	6	
Total hospital admissions (ward patients) from Jan. 1, 1935, through April 15, 1942		447,236

Therefore, the two cases herein reported are the only ones out of a series of 1,595 cases of aneurysm of the thoracic aorta at the Charity Hospital over a period of thirty-six years in which rupture of the aneurysm into the pulmonary artery occurred. There were approximately 132 ruptures during this period, so that the incidence of rupture into the pulmonary artery was only about 1.5 per cent. This is considerably below the figures (3 per cent and 3.7 per cent) presented above.

The cases of Garvin and Siegel,[11] Scott,[12] Stevenson,[13] Delp and Maxwell,[14] and White, Chamberlain, and Kelson[1] illustrated this complication in its usual form, namely, rupture into the main trunk of the pulmonary artery. In the case of Korb and Ayman,[15] however, the rupture occurred into the left pulmonary artery. This was the only instance of its kind in the literature, so that our Case 1 is the second to be reported.

This calls attention to the marked difference in the gross and microscopic changes in the right and left lungs and their respective pulmonary arteries in Case 1, and to a considerable degree in Case 2.

The right lung was much larger and firmer to palpation, and, microscopically, showed the "brown induration" of long-standing congestion. The left lung was smaller, and did not show such decided microscopic changes. The right pulmonary artery was markedly dilated and its wall thickened, as compared with the left pulmonary artery. All of these abnormalities, we believe, are attributable to long-standing pressure of the aneurysmal sac on the left pulmonary artery, with resulting stenosis of this vessel. Such an occurrence would bring about shunting of most of the blood from the right ventricle into the right pulmonary artery and right lung, and so place an overload upon these structures. When the rupture did occur into the left pulmonary artery, however, this mechanism would probably be altered.

It is believed that the rupture in Case 1 occurred some time before death, possibly during one of the patient's attacks of dyspnea and chest

pain some months previously. The pathologic changes were compatible with a rupture of some weeks' or months' duration.

The size of the heart, with cor pulmonale, has been discussed by Garvin and Siegel.[11] Cor pulmonale was well shown in Case 1, and was less marked in Case 2.

The obvious explanation is obstruction of the pulmonary artery by pressure of the aneurysm before actual communication is established. That there is, of necessity, such a period of long-continued pressure in most of these cases seems important from the standpoint of clinical diagnosis, for otherwise unexplained right ventricular hypertrophy, dilatation, or failure might thus be understood.

The clinical features of the condition have been very thoroughly discussed by Taylor,[4] as well as by more recent writers.[1, 12, 14] Suffice it to say that, in the cases herein reported, there were the usual dyspnea, pain in the chest, jerky pulse, and continuous murmur at the pulmonary valve area, with a systolic exacerbation.

The usual cause is syphilis. In Case 1 the Kline and Kolmer reactions were positive. In Case 2 there was a history of a chancre ten years previously. There was gross and microscopic evidence of syphilitic aortitis in both cases. Levaditi stains of the aortic wall and myocardium in these two cases failed to reveal spirochetes, perhaps because this examination was not carried out on fresh material. A Weigert elastic tissue stain of sections of the aortic wall in both cases showed the classical picture of disruption of the elastic fibers, with connective tissue replacement.

SUMMARY

Two cases of aneurysm of the arch of the aorta, caused by syphilis, with rupture into the pulmonary artery, are herewith reported. A brief review of the literature, with emphasis on the incidence of this condition, is presented. Attention is called to the very infrequent occurrence of this entity at the Charity Hospital of Louisiana, at New Orleans, as contrasted with the incidence given in other reports. Additional points of interest are that the rupture in Case 1 was into the left pulmonary artery, rather than into the main pulmonary trunk, and that the aneurysm of the aorta was in the transverse, rather than the ascending, portion. The gross and microscopic lesions indicated that the rupture might have been of some weeks' or months' duration. Also, our observations support the contention that there is a period of relative obstruction of the pulmonary vessel before it is eventually invaded, and that this produces changes which might aid in clinical interpretation before actual rupture occurs.

REFERENCES

1. White, P. D., Chamberlain, T. L., and Kelson, S. R.: Rupture of Aorta Into the Pulmonary Artery With Long Survival, Ann. Int. Med. **15**: 589, 1941.

2. Thurman, J.: On Aneurysms, and Especially Spontaneous Varicose Aneurysms of the Ascending Aorta, and Sinuses of Valsalva, With Cases, Med.-Chir. Tr. London **23**: 323, 1940.
3. Peacock, T. B.: Aneurysms of the Ascending Aorta Pressing Upon the Base of the Right Ventricle and Opening Into the Origin of the Pulmonary Artery, Tr. Path. Soc. Lond. **19**: 111, 1868.
4. Taylor, F.: Cases of Aortic Aneurysm Opening Into the Pulmonary Artery, Guy's Hosp. Rep. **42**: 391, 1883.
5. Kappis, M.: Die Perforation eines Aortenaneurysmas in die Pulmonalarterie, Deutsches Arch. f. klin. Med. **90**: 506, 1907.
6. Boyd, L. J.: A Study of 4,000 Reported Cases of Aneurysm of the Thoracic Aorta, Am. J. M. Sc. **168**: 654, 1924.
7. Lemann, I. I.: Aneurysm of the Thoracic Aorta; Its Incidence, Diagnosis, and Prognosis. A Statistical Study, Am. J. M. Sc. **152**: 210, 1916.
8. Potter, D. L.: Rupture of Aortic Aneurysm Into Pulmonary Artery, Tr. Chicago Path. Soc. **14**: 240, 1935.
9. Kampmeier, R. H.: Saccular Aneurysm of the Thoracic Aorta. A Clinical Study of 633 Cases, Ann. Int. Med. **12**: 624, 1938.
10. Woolley, P. G.: A Series of Ruptured Aortic Aneurysms, Am. J. Syph., Gonor. & Ven. Dis. **1**: 426, 1917.
11. Garvin, C. F., and Siegel, M. L.: Cor Pulmonale Due to Obstruction of the Pulmonary Artery by Syphilitic Aortic Aneurysms, Am. J. M. Sc. **198**: 679, 1939.
12. Scott, R. W.: Aortic Aneurysm Rupturing Into the Pulmonary Artery, Report of 2 Cases, J. A. M. A. **82**: 1417, 1924.
13. Stevenson, H. N.: Aortic Aneurysm Rupturing Into the Pulmonary Artery, With a Report of 3 Cases, Bull. Johns Hop. Hosp. **24**: 217, 1913.
14. Delp, M. H., and Maxwell, R.: Rupture of an Aortic Aneurysm Into the Pulmonary Artery, Report of a Case, J. A. M. A. **110**: 1647, 1938.
15. Korb, C., and Ayman, D.: Aortic Aneurysm Rupturing Into Pulmonary Artery; report of case, New England J. Med. **198**: 280, 1928.

THE CAPACIGRAPH-STRING GALVANOMETER FOR RECORDING ARTERIAL AND VENOUS PULSATIONS

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THE CAPACIGRAPH in combination with a galvanometer of low natural frequency has been used to record the surface displacements over the external jugular vein.[1] Substituting a string galvanometer for the galvanometer of low natural frequency provides a combination with a figure of merit which is limited only by the dynamic qualifications of the string galvanometer. The combination permits one to feed separately or simultaneously to the string galvanometer the potential variations derived from the capacigraph or from the heart. It is thus possible to make at will, and with relative ease, separate recordings of surface displacements and the electrocardiogram, or to record the resultant of the two simultaneously. When combination recordings are made, the R wave of the electrocardiogram is used as a positive (time-electrical) reference point in the analysis of complex surface displacements produced by in situ blood vessels during the cardiac cycle. The R wave may be used in this manner, but the other components of the electrocardiogram are usually not recognizable.

It is well known that the skin of the neck undergoes displacements caused by the pulsations in underlying vessels. The skin which overlies regions in which there are no large vessels also undergoes displacement during the cardiac cycle; this is caused partly by the pulsations of smaller vessels, and partly by pulsations from adjacent regions which contain large and small blood vessels. Each vessel pulsates in accordance with known tension changes which are transmitted to them and developed within them during each cardiac cycle. When the "pickup plate" is placed over the right external jugular vein, with the patient supine, a curve is obtained which has the general characteristics shown in Fig. 1. Three principal waves are recognized; they correspond to the A, C, and V of the venous pressure pulse obtained by other methods. When the pickup plate is placed over the right common carotid artery, a curve is obtained which shows the general characteristics of Fig. 2. Three waves are again recognized; however, the first is known to be auricular in origin, and shows a variable amplitude, depending upon the individual subject. So far, it has been impossible to obtain by means of the free plate approach, and under the conditions of observa-

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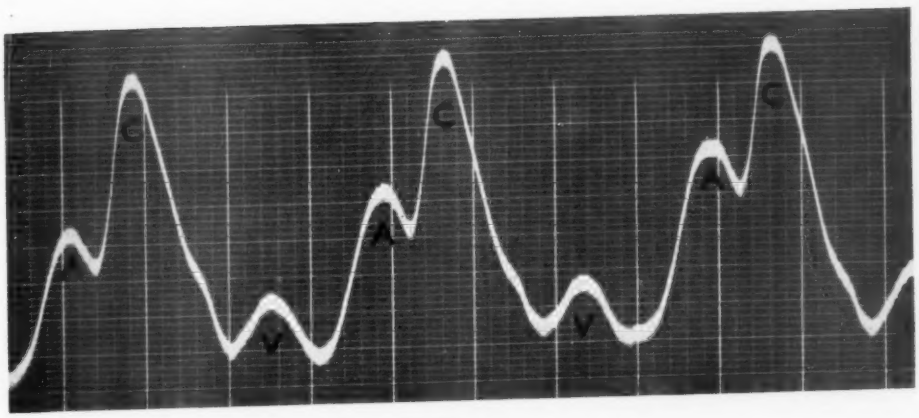


Fig. 1.

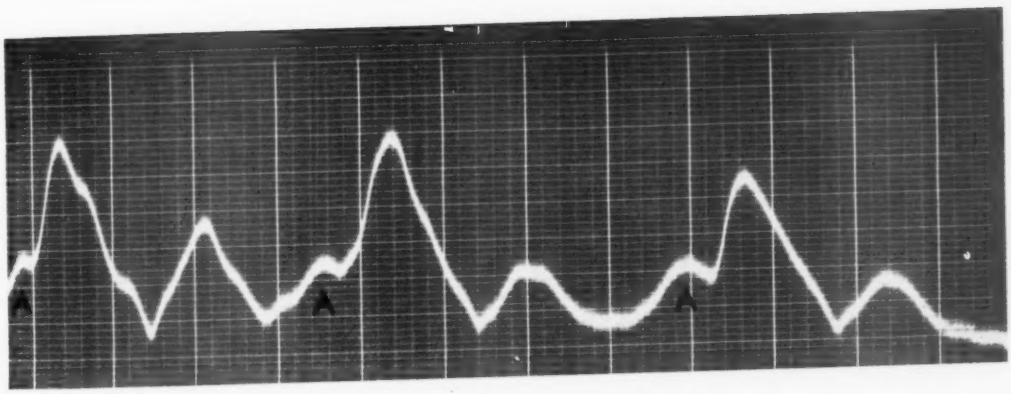


Fig. 2.

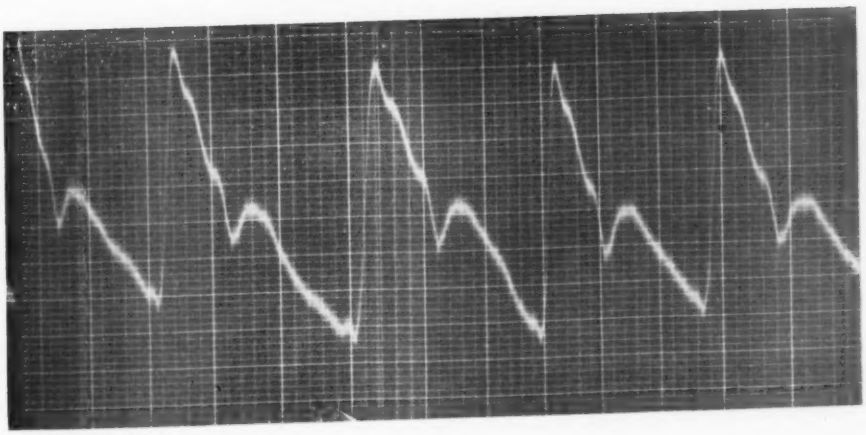
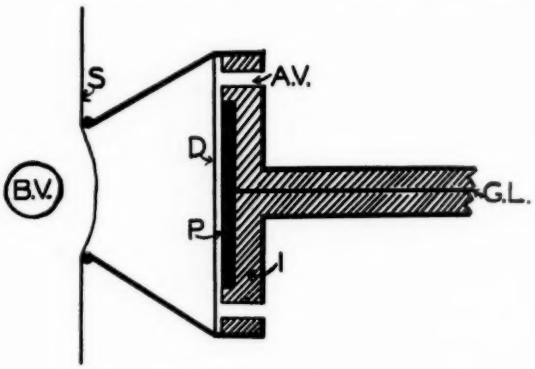


Fig. 3.

tion, an arterial neck pulsation in which there is no venous A component. On the other hand, the curve of Fig. 3 was obtained from the right common carotid region by a modified pickup plate upon which sufficient tension was applied to block the venous component. The general configuration resembles that of the arterial pressure pulse obtained by other



A.V. – AIR VENT
D – DIAPHRAM
P – PLATE
I – INSULATION
G.L. – GRID LEAD
S – SKIN
B.V. – BLOOD VESSEL

Fig. 4.

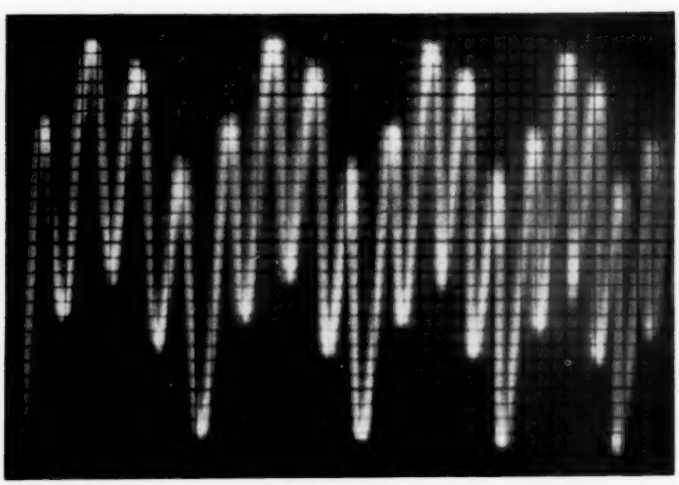


Fig. 5.

methods. The modified plate was devised on the condenser microphone principle (Fig. 4). The dynamic qualifications of this unit are good. Fig. 5 illustrates the simultaneous response to two sounds of 4000 and 16,000 V/S respectively, as registered by the cathode-ray oscillograph.

Fig. 6 shows the combined pulse and electrocardiogram which was obtained by placing the free pickup plate over the right external jugular vein. The R wave occurs during the first wave of the three-wave dis-

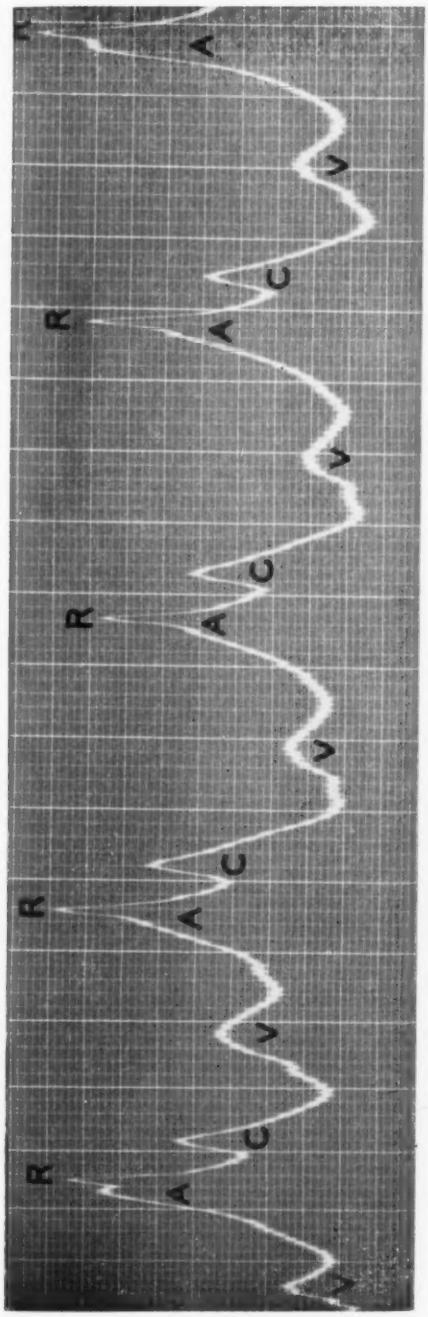


Fig. 6.

placement complex. The apparent relationship of the electrical change (ventricular in origin) and the mechanical displacement (auricular in origin) is in part due to the fact that excitation develops before the onset of the mechanical response, and in part due to the time required

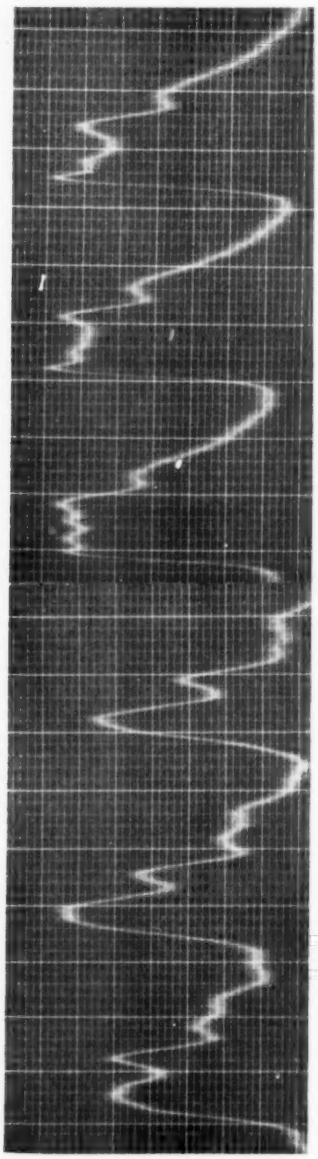


Fig. 7.

for the propagation of the pulse wave to the region underlying the pickup plate. By this means, the velocity of the pulse wave may be ascertained. The plate can be shifted nearer to, or away from, the origin of the force producing the displacement. As an index, the R wave

and its temporal relationship to a well-marked displacement component may be ascertained; then, upon shifting the plate, any change in time relationship is caused by the increase or decrease in the time necessary for the pulse wave to travel between the two points.

However, for complete accuracy, an additional factor must be taken into account: the distance through which the pulse wave is propagated may remain constant, but the interval which elapses between the development of the excitation wave and its associated electrical potentials and the mechanical response may vary. Fig. 6 bears this out. The relationship of R wave to A wave varies slightly with each beat of the heart in a cyclic manner over a period of five cardiac cycles, which, in this case, is roughly equivalent to one respiratory cycle. It is assumed that the factors which cause sinus arrhythmia produce these variations.

Fig. 7 shows the pulsatile changes which were recorded from the neck of a pregnant patient with rheumatic heart disease; the heart was 37 per cent oversize, and there were aortic and mitral lesions.

No attempt is made at this time to correlate the clinical, physiologic, and recorded data. The recordings are presented to show the potential diagnostic uses of the capacigraph-string galvanometer.

SUMMARY AND CONCLUSIONS

A new and useful method for the study of normal and abnormal cardiodynamics is presented.

REFERENCE

1. Fenning, C., and Bonar, B. E.: Additional Recordings Obtained With the Oscillato-Capacigraph, J. Lab. & Clin. Med. **25**: 175, 1939.

Special Articles

REPORT OF THE COMMITTEE OF THE AMERICAN HEART ASSOCIATION ON THE STANDARDIZATION OF ELECTROCARDIOGRAPHIC NOMENCLATURE

Introduction

IT IS nearly half a century since Einthoven first employed the letters P, Q, R, S, and T to designate the component deflections of the curves which he obtained by computing and eliminating the distortion present in records of the normal heart beat taken with the capillary electrometer. After he had invented the string galvanometer and was able to record the human electrocardiogram in undistorted form he continued to use these symbols, and eventually added to their number by assigning the letter U to the low-voltage deflection often present in early diastole, and by accepting the designation T_a, previously employed by Hering, for the inconspicuous final component of the auricular complex.

This system of nomenclature has been in practically universal use since the very beginning, and it is permanently imbedded in a vast and important literature, which all serious students of electrocardiography must frequently consult. In spite of the tremendous growth of this science in the recent past, it has continued to serve its purpose more than reasonably well. Some have found it unsatisfactory in certain respects, and have tried to replace it with an entirely different terminology, but such efforts have met with no success and are now of interest chiefly from the historical standpoint. Under these circumstances it seems essential that, in attempting to standardize electrocardiographic nomenclature, we respect usages that are long standing and generally accepted, and make only such recommendations as may be required to meet urgent needs of the present and immediate future. It is desired that all concerned clearly understand the causes of dissatisfaction which have led to a demand for some action of this sort.

Much of this dissatisfaction is clearly dependent upon the circumstance that electrocardiographic nomenclature, like any other language, is continuously changing. It must grow and expand with the science which it serves, and can be stabilized only temporarily. With the advance of knowledge the terms and symbols introduced by our predecessors have been utilized to meet new needs and have acquired meanings which they did not originally possess and which are not exactly the same for all workers. We propose to redefine those terms that are in general use so that misunderstanding may be avoided. The introduction or recommendation of new terms which have not been widely

adopted in response to an imperative need would be more confusing than helpful.

It was primarily to facilitate the description and discussion of the form of the electrocardiogram that Einthoven first assigned letters to its individual components. It is important that this function of our nomenclature should be kept in mind. The deflections to which he gave names differed one from another in various ways; in size, in direction, in shape, in duration, in sequential position, and in their relations to other events in the cardiac cycle. All the components originally named were no doubt regarded as fundamentally different in origin. It should be emphasized that neither the observed differences nor the differences in origin inferred can be considered all of the same sort or all equally significant.

It is clearly desirable that deflections alike in origin always be given the same name, and that deflections unlike in origin bear different names. Both Einthoven and Lewis after him recognized the validity and importance of this principle. The former went considerably farther than the latter in his efforts to avoid violating it, and his writings suggest that it was chiefly for this reason that he never solved to his own complete satisfaction the problem of adapting his nomenclature to electrocardiograms of unusual or abnormal outline. The difficulty seems to have been that he did not fully realize that the symbols he was using differed greatly in value; that the phenomena which they represented were by no means equal in rank.

When dealing with initial ventricular deflections conspicuously different from those to which the letters Q, R, and S were first assigned, he usually did not attempt to name them individually but made use of the symbol (QRS) to designate this group of deflections as a whole. This solution of the problem surrendered the advantages which he had gained originally by naming the components of the QRS complex.

In the case of bundle branch block of the common type, he went farther still, and often labeled the first large deflection of the essentially diphasic ventricular complex *A* and the large final deflection *B*. For a similar reason Lewis assigned the symbols Q′, R′, S′, and T′ to the components of electrocardiograms of this kind. Few authors have followed Einthoven and Lewis in giving distinctive names to the ventricular deflections of branch block curves. According to our present conceptions the final ventricular deflection always represents the same physiochemical process. By always calling it the T wave, we emphasize this important truth. By giving it one name when normal and a variety of others when abnormal we should obscure a likeness which is fundamental for the sake of making distinctions which are, by comparison, trivial. These remarks apply with equal force to the problem presented by normal and abnormal QRS complexes.

In cases of pronounced axis deviation, Einthoven used the letter R to designate the chief QRS deflection regardless of whether it was upward

or downward. Lewis, on the other hand, called this deflection R when it was upward and S when it was downward, and the vast majority of recent writers have done likewise. From time to time, however, attempts have been made to revive Einthoven's point of view.

In the last few years differences of opinion have arisen as to what constitutes a Q deflection and what an S deflection. When the QRS complex consists of a single downward deflection, some writers call this deflection S on the ground that a downward deflection should not be labeled Q unless it is followed by an upward deflection. Others call it Q on the ground that this name should be given to every downward deflection not preceded by an upward deflection.

By far the greater part of the dissatisfaction with our electrocardiographic nomenclature has clearly been due to a lack of agreement as to what principles should govern the assignment of the letters Q, R, and S to the components of the QRS complex. The symbols P, T_a, QRS, T, and U have long been used in the same way by everyone and present no difficulties. The electrocardiographic components which they represent may be regarded as at least approximately equal in rank. Each has a characteristic contour and a distinctive relation to other events of the cardiac cycle. According to our present conceptions each has a distinctive origin. The first (P) is held to represent all those electrical forces produced by depolarization (activation) of the auricular muscle; the second (T_a), all those electrical forces produced by repolarization of the auricular muscle. The third (QRS) and fourth (T) are held to represent all the electrical forces generated when these same physiochemical changes take place in the ventricular myocardium. The last (U) is less well understood; it apparently depends upon some sort of readjustment of the polarization of the ventricular muscle. Since these physiochemical changes are closely related to the mechanical activities of the heart, and necessarily occur whenever the heart beats, their electrical representatives can never be actually absent in any lead. Some may, however, be isoelectric or of such low voltage that they are imperceptible, and it often happens that a small deflection is difficult or impossible to detect because it is superimposed upon a much larger one. Whatever the standpoint adopted, each of these components of the electrocardiogram is clearly entitled to a distinctive name. It is obvious that there is little danger of mistaking one of them for any of the others.

The individual components of the QRS complex are not entities of the same sort. They vary in number from subject to subject and from lead to lead. They have not been related to different events of the cardiac cycle, nor have they been shown to depend upon the activities of distinct subdivisions of the ventricular muscle. None of them has a distinctive contour. They differ one from another chiefly in direction and in sequential position, and can not be easily defined except in terms of these differences. All these deflections are alike in origin

in the sense that all are produced by electric forces generated by the spread of the excitatory process over the ventricular muscle. They can differ in origin only as regards the particular fraction of these forces which each represents. The individual fibers which contribute the elementary forces responsible for a given component in a given lead do not all lie in the same part of the ventricular myocardium. None of the QRS components in any lead has a simple anatomical basis of this kind which would make its origin distinctive in the anatomical sense. The origin ascribed to any component is mainly, for this reason, dependent to a large extent upon the point of view adopted, and no one particular point of view has gained such wide acceptance as to make it pre-eminent.

It has been suggested that the QRS interval should be subdivided in one way or another, and that names should be assigned to parts of the QRS complex solely on the basis of the particular subdivision of this interval within which they fall, rather than to the separate deflections of which it is composed. This suggestion is derived from the view that any part of the QRS complex written during a given interval of time in one lead is identical in origin with those parts of the QRS complex written during the same interval in other leads in the sense that it is produced by the same electrical forces. It is assumed that all the elementary electric forces present at a given instant are equally effective, in proportion to their magnitude, in all the leads under consideration, or that, so far as these leads are concerned, they are equivalent to a unique resultant electromotive force which may be substituted for them. Einthoven's equilateral triangle defines a resultant electromotive force, the cardiac vector, which may be substituted for the actual electromotive forces when dealing with limb leads, if the assumptions upon which this triangle is based may be regarded as representing the true situation with sufficient accuracy for the purposes in mind. Now that it is customary to take precordial leads to which it is not applicable, as well as limb leads, it is not desirable to enthrone this point of view in our nomenclature and disregard others which are equally legitimate.

For this reason, and because it greatly complicates the assignment of the letters Q, R, and S to the initial group of ventricular deflections and the description of the form of the QRS complex, we believe that a downward deflection should never be labeled R on the ground that it occupies the same interval and represents the same resultant forces as an upward deflection in another lead to which this letter has been appropriately assigned. It is equally disadvantageous to label an upward deflection Q or S because it corresponds in time to a downward deflection in another lead to which the same letter has previously been allotted.

The considerations mentioned and the multiplicity of leads now in use fully justify the labeling of the QRS components of one lead without reference to the number or character of the QRS components in any

other lead. The allocation of the symbols employed should be determined solely by the direction and sequence of these deflections in the lead under consideration.

RECOMMENDATIONS

1. The symbols P, T_a, QRS, T, and U should be used to represent those deflections or groups of deflections to which they were originally assigned, both when the electrocardiogram is normal and when it is abnormal.

2. In the majority of cases the QRS complex is superimposed upon the T_a deflection. For this reason the level of reference from which the voltage of the QRS deflections is measured should be the level at which the first of these deflections begins. The voltage of an upward QRS deflection should be measured by estimating the vertical distance between the upper edge of the trace at the beginning of the QRS interval and the upper edge of the trace at the point where the deflection reaches its maximal elevation. The voltage of a downward deflection should be determined by estimating the vertical distance between the lower edge of the trace at the beginning of the QRS interval and the lower edge of the trace at that point of the deflection which is farthest from the reference level.

3. In order to indicate how the QRS complex should be subdivided for the purpose of assigning symbols to the deflections which it displays, we may describe a QRS complex which has three components in the following terms: The first deflection begins at the onset of the QRS interval when the trace first leaves the reference level. From this point the trace rises or falls to a turning point, where the direction of its motion is reversed. It may pass through a second or third turning point before crossing to the opposite side of the reference level.* At this crossing the first deflection ends and the second begins. The second deflection, necessarily opposite in direction to the first, must display one turning point and may display many; it does not end until the trace crosses the reference level for the second time. The third deflection begins at the second crossing and ends at the RS-T junction. No part of the QRS complex which does not display at least one turning point should be considered a separate deflection. If the RS-T junction is displaced and this junction and the last turning point lie on opposite sides of the reference level, that portion of the trace which lies between the last crossing and the RS-T junction should be considered part of the deflection to which the last turning point belongs.

The earliest QRS deflection which lies above the reference level should be labeled R. Any downward deflection which precedes R, so defined, should be labeled Q. The first of any downward deflections which may

*When the trace is descending it crosses the reference level at the instant when its lower margin reaches a position below that which it occupied at the beginning of the QRS interval. When the trace is ascending it crosses the reference level at the instant when its upper margin reaches a position above that which it occupied at the beginning of the QRS interval.

follow R should be labeled S. The first of any upward deflections which may follow S should be labeled R′, and the first of any downward deflections which may follow R′ should be labeled S′. If it is necessary to label still later deflections of the QRS group, the symbols R,″ S,″ etc., should be used in accordance with the same principles. When R is absent, so that the QRS complex consists of a single downward deflection, this deflection should be labeled QS. In statistical studies QS, Q, and S deflections should be considered separately.

A deflection is "notched" when it displays more than one turning point on the same side of the reference level. A deflection is "slurred" when it displays a distinct and local "thickening" on either limb or at its apex, due to a sudden and pronounced change in the slope of the curve, or, in other words, in the rate at which the trace is rising or falling.

When the form of the QRS complex varies from moment to moment because of the effect of the respiratory movements upon the position of the heart, or for some similar reason, the classification of this complex should be determined by the variety of complex which is most abundant, or, if no type is numerically predominant, by the outline of the complexes which are of intermediate form. Very small QRS complexes (largest deflection less than 5 mm.) which display more than three components or multiple slurring and notching should be classed as "small and bizarre" or "vibratory."

4. The term RS-T junction should be used to indicate the point or shoulder which marks the end of the QRS complex, i.e., the point where the steep slopes of the QRS deflections are more or less abruptly replaced by the more gradual slopes which precede or comprise the first limb of the T wave. In many electrocardiograms the RS-T junction is followed by a nearly horizontal or gently sloping segment which lies on, above, or below the reference level, and ends with the onset of a much steeper slope that rises or falls to the apex of T. It is agreed that the term RS-T segment is a useful name for this part of the ventricular complex when it exists, even though it is proper to regard it as the earliest part of the T deflection. When there is no point between the RS-T junction and the apex of T at which a sharp change in the slope of the trace occurs, this part of the ventricular complex should be called the first limb of the T wave. When the term RS-T segment is used without reference to some particular electrocardiogram or to some particular class of electrocardiograms, it should be understood to refer merely to that part of the ventricular complex which immediately follows the RS-T junction. The reference level for the measurement of the displacement of the RS-T junction should be the same as the level of reference for the measurement of the QRS deflections. The level of reference for the measurement of the RS-T segment, the T wave, and the U wave should be the isoelectric level when this can be determined; otherwise it should be the level of the

trace at the beginning of the QRS interval. The isoelectric level is the level of the trace at the beginning of the P wave when the P wave occurs in its normal relation to the QRS deflections and is not superimposed on T or U.

5. The term "diphasic T waves" should be applied to those final ventricular deflections which present two distinct turning points, one on each side of the level of reference. If the earlier turning point lies below this level, and the latter above it, the diphasic T wave may be said to be of the minus-plus (− +) type. If the reverse is the case, it may be said to be of the plus-minus (+ −) type. When the term diphasic is used with reference to other deflections, to the QRS complex, or to the ventricular complex as a whole, it should be used in the same sense.

6. When applied to the QRS complex, the T deflection, to any other electrocardiographic component, or to RS-T displacement, the term "concordant" should signify that the largest deflection or displacement is in the same direction in Lead III as in Lead I. Under the same circumstances the term "discordant" should signify that the largest deflection or displacement in Lead III is opposite in direction to that in Lead I.

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SECOND SUPPLEMENTARY REPORT BY THE COMMITTEE OF THE AMERICAN HEART ASSOCIATION FOR THE STANDARDIZATION OF PRECORDIAL LEADS

EARLY in 1938 the Committee of the American Heart Association for the Standardization of Precordial Leads and a similiar committee representing the Cardiac Society of Great Britain and Ireland made joint recommendations with reference to a single precordial lead for routine use. In a supplementary report published in the same year,* the American committee recommended that when multiple precordial leads were taken the precordial electrode be paired either with an electrode on the left leg or with a central terminal connected through equal resistances of 5,000 or more ohms to three electrodes, one on the right arm, one on the left arm, and one on the left leg. Six precordial points were recommended as suitable locations for the precordial electrode,† and these may be referred to as the C_1, C_2, C_3, C_4, C_5, and C_6 positions. In the last few years, the number of electrocardiographers who have abandoned single in favor of multiple precordial leads has rapidly increased, but there has been no uniformity as regards the number of leads taken, the location of the remote electrode paired with the precordial electrode, or the locations of the precordial points regularly explored.

There has been a persistent demand that some further action be taken with reference to the standardization of precordial leads. The undersigned have, therefore, consulted, and have attempted to reach an agreement with reference to the more important questions that have arisen in connection with this problem. It is agreed that many of these questions must be left unanswered until our knowledge of the precordial electrocardiogram is far more complete than at present. A great deal of methodical painstaking work is urgently needed with reference to the best location for the remote electrode, the desirability of taking precordial leads routinely, and the best combination of locations for the precordial electrode. The present situation is not, however, due solely to inadequate information but also to a lack of complete agreement as to exactly what is meant by "best combination" and

*AM. HEART J. 15: 235, 1938.

†It has been pointed out to us that the meaning of the last sentence of the third paragraph of our previous supplementary report is not clear. The correct interpretation of this sentence is as follows:

When the letters and subscripts specified are employed, it shall be understood that in the case of the sternal leads the precordial electrode has been placed in the 4th intercostal space, and that in the case of the other leads it has been placed upon a line drawn from the left sternal margin in the 4th intercostal space to the outer border of the apex beat and continued around the left side of the chest at the level of the apex beat. When the apex beat cannot be satisfactory located, this line should be drawn from the left sternal margin in the 4th intercostal space to the point where the left midclavicular line crosses the center of the 5th intercostal space, and should be continued around the left side of the chest at the level of this point.

similar terms when used with reference to precordial leads, and as to whether the questions at issue are to be decided on empirical grounds alone or, if not, as to what basic principles should be given important consideration. The recommendations which follow must, for these reasons, be considered merely tentative.

The Committee is agreed that a single precordial lead from the region of the cardiac apex, or from any other part of the precordium, is inadequate. When multiple precordial leads are taken, it is found that in the vast majority of cases the extreme right side of the precordium and the extreme left side of the precordium yield QRS complexes of more or less opposite form. Leads from a usually small region lying between those from which complexes of opposite types are obtained customarily yield complexes of intermediate or transitional form, which are often difficult to interpret when curves from points farther to the right and from points farther to the left are not available for comparison. The location and size of the region from which transitional complexes are obtained vary greatly from case to case, and are not entirely constant in one and the same subject. When single precordial leads are taken from the outer border of the apex beat, the exploring electrode is, in actual practice, sometimes placed to the right of the region of transition mentioned and sometimes to the left of it, or within it. In serial observations on the same subject inaccuracy in placing this electrode or an alteration in the size or location of the region in question may be responsible for striking changes in the form of the curve obtained by what is technically the same lead.

This is only one of the causes for dissatisfaction with routine apical leads. When all cases are considered, regardless of whether the standard leads are normal or abnormal, it is perhaps true that a lead from the region of the apex or from the left anterior axillary line at the level of the apex will display abnormalities of the ventricular complex more often than any other single precordial lead. When, however, only those cases in which the limb leads are normal are considered, this is certainly not the case. It is now clear that when the standard limb leads are normal, the precordial leads most likely to yield significantly abnormal curves are those from points lying between the left sternal border and the midclavicular line. Consequently, single apical leads most often fail completely in those cases in which multiple precordial leads have most to offer.

The Committee believes that three is the least number of precordial leads that can be regarded as satisfactory for general purposes. It suggests that those who wish to reduce the number of such leads to a minimum take leads from the C_1, C_3, and C_5 positions. All are urged to take additional leads whenever possible. A lead from the C_2 or a lead from the C_4 position may show diagnostic abnormalities when equally significant changes fail to occur in other leads. Those who follow our recommendations must remember that inversion of the T

deflections in leads from the C_1 position is frequently encountered in normal adult subjects. It is believed that those who have had little experience with multiple precordial leads would gain much worthwhile information by taking a full set of six precordial leads on a few normal subjects and on a series of patients with known cardiac abnormalities of the commoner types.

It is agreed that the information available does not permit a definite decision on empirical grounds as to the best location for the remote electrode with which the exploring or precordial electrode is paired. It is recommended that the precordial electrode be paired with an electrode on the right arm, with an electrode on the left leg, or with a central terminal connected through equal resistances of 5,000 or more ohms* to three electrodes: one on the right arm, one on the left arm, and one on the left leg. Some, but not all, members of the Committee who formerly placed the remote electrode on the left leg now prefer to place it on the right arm. It has been observed that when the precordial electrocardiogram is judged by the normal standards at present available, a lead from a given point on the precordium may yield an abnormal curve if the exploring electrode is paired with a left leg electrode (CF lead) even though the curve obtained from the same point by using the right arm electrode as the reference point (CR lead) is within normal limits. The opposite situation may also arise. It has also been observed that in certain cases of cardiac infarction in which diagnostic changes are present in the standard limb leads, CF leads display the most striking, and CL leads (leads from the precordium to a left arm electrode) the least striking, changes. These observations can not, however, be interpreted as indicating that CF leads are always more reliable in the diagnosis of infarction than precordial leads of other kinds. There will be less confusion with reference to the effect of the remote electrode if it is clearly understood that each CR lead is equal to the corresponding CF lead plus standard Lead II; that each CL lead is equal to the corresponding CF lead plus Lead III; and that each central terminal lead is equal to the corresponding CF lead plus one-third the sum of Leads II and III, and is the algebraic mean of the CR, CL, and CF leads from the same precordial point.

The Committee does not desire at this time to make any recommendation bearing on the question as to whether precordial leads should be taken routinely or in selected cases only. It believes that precordial leads are most likely to yield information of diagnostic importance under the following circumstances: (1) Whenever myocardial infarction is suspected or must be considered a possibility; (2) whenever myocardial disease is suspected or must be considered a possibility and

*Recent observations indicate that in the vast majority of cases, if not in all, the omission of these resistances has no appreciable effect upon the form of the precordial curves obtained. Consequently, it may be satisfactory to connect the central terminal directly to the three extremity electrodes without the use of intervening resistances of any kind. Further studies should be made before this method is generally adopted.

other methods of examination yield no unequivocal evidence of cardiac disease; (3) whenever it is important to distinguish between right and left ventricular hypertrophy or between right and left bundle branch block and this can not be satisfactorily done by other means; (4) whenever for any reason a complete cardiac study is indicated.

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Clinical Reports

A CASE OF TRICUSPID INSUFFICIENCY WITH UNUSUAL VENOUS PULSATIONS IN THE EXTREMITIES

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DISEASE of the tricuspid valve and its clinical aspects have been described and discussed fully, and the criteria for diagnosis have been clearly outlined.[1-8] Pulsation of the neck veins is one of the important features of the syndrome. However, pulsations of the veins in the extremities have been less frequently noted, and especially pulsations in the veins of the lower extremities, the occurrence of which is apparently much less common. We have recently had the opportunity of observing a patient with tricuspid insufficiency who presented remarkable pulsations in varicose veins of the legs, and the apparent rarity of this condition seems to warrant this report.

CASE REPORT

S. M., a 52-year-old Jewish housewife, was admitted to another hospital January 19, 1933, complaining of cough and fever. Two weeks before, she had had an attack of pain in the chest which was typical of coronary occlusion. She had been improving until the day before admission, when she developed a cough and a rise in temperature to 103.6° F. Physical examination revealed cardiac enlargement without murmurs, but over the middle of the sternum there was a scratchy systolic sound which was thought to be a pericardial friction rub. There was consolidation of the upper lobe of the left lung, and a small amount of fluid was present at the base of the left lung. The liver was not enlarged and there was no peripheral edema. She was discharged after a hospital stay of forty-eight days. The diagnosis was coronary thrombosis and infarction of the left lung.

The patient was readmitted to the same hospital four years later because of congestive heart failure. The heart was enlarged as before. At this time a blowing systolic murmur at the apex, a rough systolic murmur at the base, and a blowing diastolic murmur at the aortic area were described. The heartbeat was totally irregular. The liver was enlarged, smooth, and soft, but did not pulsate. There were slight edema of the extremities and large varicose veins of the legs. The edema disappeared, but hepatomegaly persisted, and, after six weeks, she was discharged and advised to remain in bed.

She was admitted to the same hospital, for the third time, four months after her second admission, again with congestive heart failure. Examination revealed marked arterial pulsations in the neck, but there was apparently no venous engorgement. At this time systolic and diastolic murmurs were heard at both the apex and the base. While in the hospital an intrinsic pulsation of the liver was noted for the first time, and, although the other gross signs of cardiac insufficiency

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disappeared, the liver was still very large and pulsated vigorously at the time of discharge.

She was first admitted to the Baltimore City Hospital September 1, 1941, on the service of Dr. John T. King, Jr., approximately four years after her last admission to the other hospital, or eight years and nine months after the onset of her illness. In the interval between discharge from the other hospital and admission to the Baltimore City Hospital, she had maintained a semi-invalid existence at home. However, she had gotten along fairly well without being completely incapacitated until about three months before admission, when she began having increasingly severe edema of her legs. About one month before admission she had noted swelling of her abdomen. She had only moderate dyspnea on exertion, and this was not an outstanding complaint, but for several weeks she had had attacks of breathlessness at night. Three weeks before admission she began to have a persistent, brassy cough which was productive of thin, mucoid sputum. Because she did not improve after treatment was instituted by her family physician, she was referred to this hospital. Physical examination revealed a poorly developed, emaciated, elderly woman with moderate respiratory distress, who appeared to be chronically ill. The blood pressure on admission was 90/50, and, during the hospital stay, varied between 90/50 and 130/90. The mucous membranes were pale and the tongue was pale and smooth. The pupils reacted normally. Examination of the ocular fundi by an ophthalmologic consultant revealed that the optic discs were normal. The retinal arteries were slightly constricted, but well within the normal limits for her age. The right disc showed a blanching which was synchronous with the pulse; this was thought to be caused by compression of the vein, as it crossed the disc margin, by the corresponding artery. No definite pulsation of the retinal veins was seen. The jugular veins were greatly dilated and distended up to the level of the mandible, and pulsated vigorously. There were dilated, pulsating veins on each side of the sternum. The breath sounds were vesicular. There were signs of pleural effusion on the right, and many râles at the bases of both lungs. There was a systolic retraction at the apex of the heart, with a rotating impulse and an irregular rhythm. There was no thrill, shock, reduplication, or gallop. The cardiac dullness extended to the anterior axillary line on the left. There was an area of dullness over the manubrium which extended three fingerbreadths to the left, but did not extend past the midline toward the right. With the patient on the right side the right border of the heart shifted two centimeters. However, there was no shift of the left border with change in position. The first sound at the apex was absent. There was a harsh, very low-pitched, apical systolic murmur, and a diminuendo mid-diastolic murmur was heard inside the apex at the left sternal border. On several occasions a mid-diastolic rumble was heard at the cardiac apex, but this was not constant. There were a coarse, low-pitched aortic systolic murmur and a softer diastolic aortic murmur. At the tricuspid area there was a grating, low-pitched, systolic murmur very similar to that heard at the mitral area. The pulmonic second sound was rather coarse. There were a few extrasystoles, but fundamentally the rhythm was regular. The liver was palpable two fingerbreadths below the level of the umbilicus. It was slightly tender and rather soft. There was a striking intrinsic pulsation of the liver. No murmur was heard over it. The abdomen was symmetrically distended and there was edema of the abdominal wall. Shifting dullness in the flanks and suprapubic dullness were present, but there was no demonstrable fluid wave. There was marked, soft edema of the legs and thighs and over the sacrum and chest wall, and a superficial ulceration was present over the right leg. As the patient improved and began to lose edema, large varicose veins of both legs became evident. There was an enormously dilated vein in the right leg which pulsated vigorously and over which a thrill could be felt. There was another pulsating vein in the left leg; it was not as large as that on the right, but

over it a loud systolic murmur could be heard. No murmur was heard in the popliteal space, and femoral arterial pulsations on both sides were vigorous.

Examination of the blood revealed a moderate hypochromic anemia. Chemical studies of the blood showed nothing abnormal. Urinalysis was negative except for a one-plus reaction for albumin. A roentgenogram of the chest showed great enlargement of the heart and calcification of the aorta. There was a large hydrothorax on the right, with congestive changes in both lungs. Fluoroscopic examination revealed that both the right and left sides of the heart were enlarged; both borders moved in very slow but forceful pulsations. The same pulsations were noted along the right side of the diaphragm, where they had a downward direction. The pulsations of the aorta were less in amplitude. There was no definite evidence of pulsation along the right border of the upper part of the mediastinum. These ob-

Fig. 1.—The roentgenkymogram shows pulsations of increased amplitude, especially in the region of the right ventricle. The ventricular pulsations are slightly irregular in amplitude. The pulsations of the aorta, superior vena cava, and the diaphragm are synchronous and large.

servations were interpreted as being indicative of disease of the tricuspid valve, with hepatic pulsation. Roentgenkymographic examination of the heart (Figs. 1 and 2) revealed that the heart was enlarged in all its diameters. The right ventricle was markedly enlarged and showed increased pulsations. These pulsations were slightly irregular in amplitude. The pulsations of the diaphragm, aorta, and superior vena cava were synchronous and large in amplitude. All this again suggested disease of the tricuspid valve. The venous pressure, measured with the skin of the back in the interscapular area as the reference point,[9] was persistently elevated, in both the arms and legs. In the arms the venous pressure varied between 90 and 170 mm. of saline above the normal, and in the femoral veins it remained at about 200 mm. of saline above the normal level. There was a systolic pulsation in the manometer of 10 to 20 mm. of saline with the needle in either the antecubital or femoral vein. The circulation rates were increased.[10, 11] The arm-to-tongue time varied between

27 and 46 seconds, and the arm-to-lung time varied between 11 and 15 seconds. Electrocardiograms on admission showed left axis deviation, a rate of 70, a P-R interval of 0.2 second, a QRS interval of 0.11 second, depression of S-T in Lead I, and elevation of S-T in Leads III and IV; T was diphasic in Leads I, III, and IV, and upright in Lead II. What were thought to be P waves were seen in Leads II and I, and therefore the record was interpreted as showing nodal rhythm with left bundle branch block. Numerous subsequent records showed essentially normal rhythm, with what were thought to be P waves in Leads II and III. Leads from the sternal region did not show definite P waves, and in several records there appeared to be definite F waves. Ectopic ventricular beats were frequent. A review of all the records resulted in an interpretation of auricular fibrillation and complete heart block.

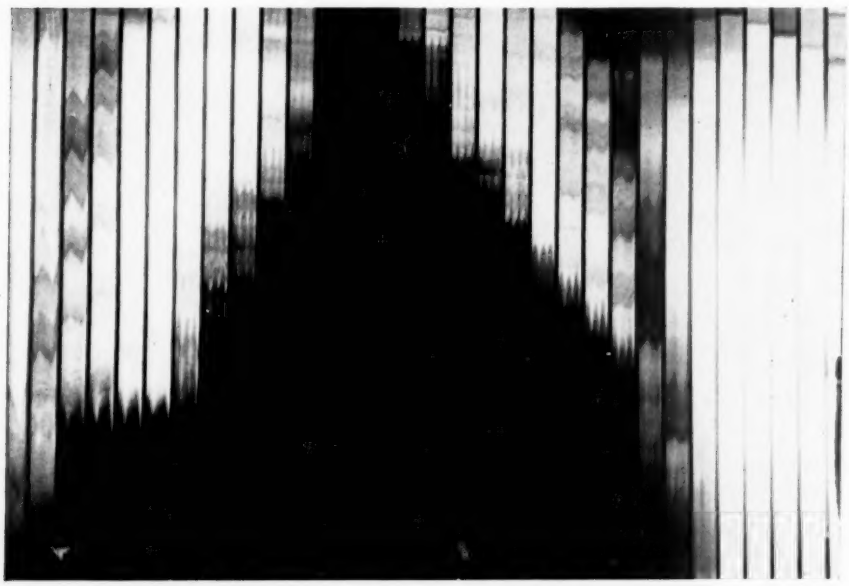

Fig. 2.—Roentgenkymogram which shows the pulsations of the diaphragm transmitted from the underlying liver. The diaphramatic pulsations are synchronous with those of the aorta and superior vena cava.

The patient was digitalized and given mercurial diuretics. Two thoracenteses were performed. She improved slowly, but tolerated digitalis very poorly, and it was discontinued. Without digitalis, her pulse rate ranged between 70 and 80. While under the influence of the drug it remained between 50 and 60, and the patient was quite uncomfortable. After six weeks in the hospital she became almost entirely free of edema. However, the liver remained large and continued to pulsate, and the veins in the neck and the varicose veins in her legs continued to be distended and to pulsate vigorously. After six weeks she had improved enough to be sent to a nursing home for further care.

This report is incomplete in that a definite statement concerning the cause of the heart disease cannot be made, and, since the patient is still alive, autopsy confirmation of clinical impressions is lacking.* It can be said, in brief review, that a 60-year-old woman, eight years earlier,

*After this paper was submitted for publication the patient died in a convalescent home. Permission for autopsy was not obtained.

without previous cardiac complaints, experienced a sudden attack of substernal oppression and collapse that was regarded as indicative of myocardial infarction. Subsequently she was thought to have had pulmonary infarction. No heart murmurs were recorded by competent observers at that time. During the ensuing eight and three-quarters years she had been limited to a semi-invalid existence because of cardiac insufficiency, and had been hospitalized twice because of heart failure, on which occasions the progression of the degree of heart failure and the development of various cardiac murmurs had been noted. Four years before admission to the Baltimore City Hospital her liver was found to be enlarged and pulsating, but it was not until her last hospital admission that the extreme pulsations in the varicose veins of her legs had become evident and the diagnosis of tricuspid insufficiency was considered.

It is difficult to conceive of rheumatic valvular disease of such extent developing in a 60-year-old person who was known to have had no cardiac murmurs at the age of 52. That this patient had arteriosclerotic heart disease, possibly one or more myocardial infarctions, and marked cardiac dilatation and hypertrophy of long standing seems probable. The development of cardiac murmurs can be explained by cardiac dilatation and valvular sclerosis, and possibly calcification. A further possibility is that there was an embolus in one of the larger branches of the pulmonary artery at the onset of her illness, with the subsequent development of pulmonary hypertension and right-sided heart strain, and that this was responsible for the clinical manifestations at the time of her admission to this hospital. It is the pulsation in the varicose veins of the legs which is of greatest interest, and with this we are primarily concerned in this report. Although pulsations in the cervical veins almost always accompany tricuspid disease, similar pulsations in the veins of the extremities are less common. Kerr and Warren[12] noted pulsations in the veins of the arms and on the dorsum of the hand in a series of patients with heart failure and relative tricuspid insufficiency, and such pulsations in the larger veins of the upper extremities have been noted by others, but visible and palpable pulsations in the veins of the lower extremities are less common. According to Kerr and Warren,[12] Friedreich, in 1866, reviewed the literature thoroughly for venous pulsations in the extremities, and he cited Marey, who, with Gaubler and Verneuil, noted pulsations in varicose veins of the leg in one case. Teufl,[13] in 1936, in a study of 32 cases of pulsating veins of the extremities, found 16 cases of pulsating varicose veins. This would seem to indicate that such pulsations in the lower extremities are not at all rare, but rather are either overlooked or neglected. Hallock and Clarke[14] have recently reported a case of pulsation in the veins of the neck, retinae, and upper extremities, and in varicose veins of the lower extremities.

In our case, no pulsation could be seen in the veins of the ocular

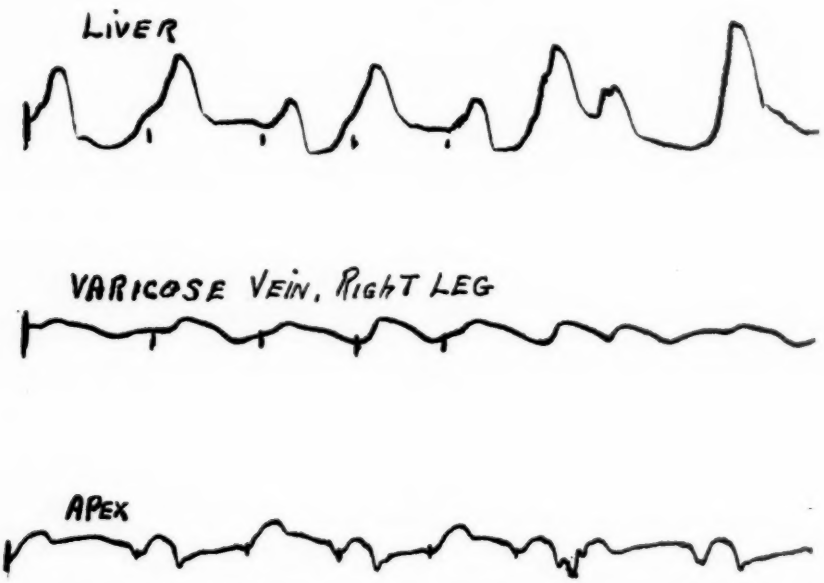

Fig. 3.—Polygraphic tracing made from the apex beat, the liver, and the varicose vein of the right leg.

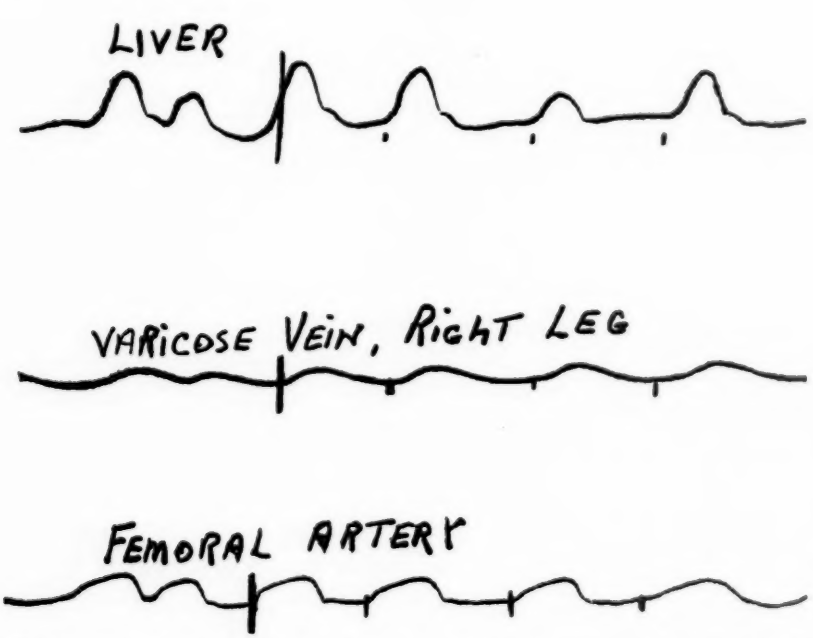

Fig. 4.—Polygraphic tracings from the femoral artery, varicose vein of right leg, and the liver. The large vertical lines on the left of each tracing indicate the starting positions of the writing pens.

fundi, and there were but slight visible pulsations of the distended veins of the arms. However, there were marked and vigorous pulsations of the cervical veins and in the varicose veins of both legs. The pulsation of the liver could be seen from a distance of several feet.

Polygraphic tracings were made from the cardiac apex, carotid artery, jugular vein, liver, femoral artery, and the varicose veins of the leg. The liver and leg vein pulses were found to correspond with the apex beat, and there was a similar relationship between the pulsation in the

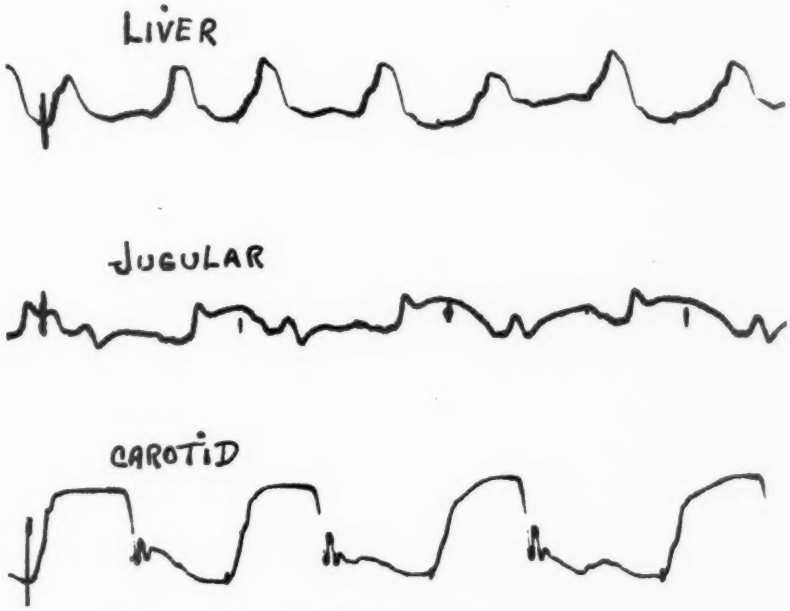

Fig. 5.—Polygraphic tracings from the carotid artery, jugular vein, and liver, showing a 2:1 ratio of the arterial and venous pulsations.

liver and leg veins and that in the femoral artery (Figs. 3 and 4). The temporal relations of the apex beat and liver and venous pulses varied slightly, but this was thought to be an artifact. The conclusion was drawn that the ventricular contractions originated the venous deflections.

In one record, on which, unfortunately, no apex tracing was made, the liver and carotid pulses had a 2 to 1 ratio (Fig. 5). This was interpreted as meaning that, at that time, the insufficiency of the tricuspid valve and the force of the ventricular beat were such that complete regurgitation through the incompetent tricuspid valve, rather than opening of the aortic valve and ejection into the aorta, occurred every second beat. Subsequent tracings failed to show this phenomenon; instead, there was always a 1 to 1 ratio of the apex, carotid, and liver pulsations. In a few tracings from the jugular vein, small deflections preceding what appeared to be C waves were noted. However, they were never clear

enough or large enough to be definitely called waves, and no clear evidence of auricular activity was ever obtained.

The venous pressure in the antecubital and femoral veins was always elevated, even after the cardiac status of the patient had improved and she had become free of peripheral edema and gross pulmonary congestion. Likewise, the circulation times were persistently prolonged, although the arm-to-lung circulation time was but moderately increased as compared with the arm-to-tongue time; the latter was consistently 2 to 3 times larger than normal. This was surprising, in view of the outstanding evidence that the heart failure was predominantly right-sided.

CONCLUSION

A case of tricuspid insufficiency with venous pulsation in the neck, a markedly pulsating liver, and pulsation in varicose veins of the legs is presented.

We are indebted to Dr. E. J. Leopold, of Sinai Hospital, Baltimore, Maryland, for permission to examine the records of this patient's admission to that hospital. Dr. C. McC. Brooks, of the Physiology Department of the Johns Hopkins Medical School, was kind enough to interpret the polygrams.

REFERENCES

1. Altschule, M. D., and Blumgart, H. L.: The Circulatory Dynamics in Tricuspid Stenosis, AM. HEART J. **13**: 589, 1937.
2. Altschule, M. D., and Budnitz, E.: Rheumatic Disease of the Tricuspid Valve, Arch. Path. **30**: 7, 1940.
3. Clements, Alfred B.: Isolated Tricuspid Stenosis of Probable Rheumatic Origin, Am. J. M. Sc. **190**: 389, 1935.
4. Dressler, W.: Pulsations of the Wall of the Chest Associated With Tricuspid Regurgitation, Arch. Int. Med. **60**: 441, 1937.
5. Friedlander, R. D., and Kerr, W. J.: Clinical Diagnosis of Tricuspid Stenosis; Report of a Case Complicated by Paroxysmal Nodal Tachycardia and A.V. Dissociation, AM. HEART J. **11**: 357, 1936.
6. Taussig, Barret L.: A Case of Tricuspid Stenosis With Enormous Dilatation of the Right Auricle, AM. HEART J. **14**: 744, 1933.
7. Young, J. J., and Cotter, L. H.: Tricuspid Stenosis and Tricuspid Insufficiency, New York State J. Med. **112**: 798, 1920.
8. Zeisler, E. B.: Tricuspid Stenosis, AM. HEART J. **8**: 697, 1933.
9. Lyons, R. H., Kennedy, J. A., and Burwell, C. S.: Measurement of Venous Pressure by the Direct Method, AM. HEART J. **16**: 675, 1939.
10. Baer, S.: Clinical Application of the Determination of the Circulation Time, Ann. Int. Med. **13**: 2246, 1940.
11. Bernstein, M., and Simpkins, S.: Use of Magnesium Sulfate in the Measurement of the Circulation Time, AM. HEART J. **17**: 218, 1939.
12. Kerr, W. J., and Warren, S.: Peripheral Pulsations in the Veins in Congestive Failure of the Heart, Associated With Pulsation of the Liver and Tricuspid Regurgitation, Arch. Int. Med. **36**: 593, 1928.
13. Teufl, Robert: Pulsation normaler und variköser Extremitätenvenen und ihre diagnostische Bedeutung, Wien. med. Wchnschr. **86**: 288, 352, 407, 436, 1936.
14. Hallock, P., and Clarke, W. O.: Significance of Generalized Systolic Pulsation of Veins, With Report of Case in Which There Was Marked Pulsation of Varicose Veins, AM. HEART J. **22**: 410, 1941.

ENDOCARDITIS CAUSED BY THE MICROCOCCUS PHARYNGIS SICCUS: RECOVERY AFTER TREATMENT WITH HEPARIN AND SULFAPYRIDINE

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ENDOCARDITIS caused by the *Micrococcus pharyngis siccus,* which is ordinarily a nonpathogenic inhabitant of the upper respiratory tract of man, has been reported four times.[1-4] Endocarditis caused by closely related organisms which may be indistinguishable bacteriologically[5] from the *Micrococcus pharyngis siccus* is also rare; one case of *Micrococcus catarrhalis* endocarditis,[6] two cases of *Micrococcus pharyngis flavus* endocarditis,[7, 8] and two cases of endocarditis caused by similar, but not identical, Gram-negative cocci[9, 10] have been reported.

We are reporting an additional case of endocarditis caused by the *Micrococcus pharyngis siccus.* This patient, unlike any previously reported, is apparently cured. One year after her acute illness she was alive and well. Recovery occurred during November, 1940, while heparin and sulfapyridine therapy was being employed. The clinical diagnosis was based upon the following evidence: (1) multiple embolic phenomena, manifested by meningitis, attacks of acute, left-sided, upper abdominal pain, occasional erythrocytes in the urine, crops of white-centered petechiae involving the mucous membranes, retinae, and finger tips; (2) a changing heart murmur; (3) two positive blood cultures for *Micrococcus pharyngis siccus* before treatment was begun; and (4) the absence of a demonstrable focus for emboli other than the heart.

CASE REPORT

H. J. (X-15339), a 14-year-old, colored schoolgirl, was admitted to the Detroit Receiving Hospital Oct. 16, 1940, in an irrational and semiconscious condition.

The patient had apparently been well until Sept. 28, 1940, eighteen days before her admission to the hospital, when, on the last day of her menstrual period, she developed a dull, frontal headache and felt feverish. These symptoms were attributed to playing too long in the sun without a hat. The headache persisted, and radiated from behind the left eye across the forehead and to the vertex. On the second day of her illness blurring of vision appeared. After she had been ill about a week without improvement, she was seen by a physician. He reported a temperature of 103° F., diagnosed "acute sinusitis," and advised rest in bed.

During the second week, the patient's condition grew worse. Her headache became more severe, the blurring of vision was more marked, and her neck became stiff. She continued feverish, and, for five or six days, vomited all solid food, and most liquids. Finally she became semistuporous and irrational. She was again seen by a physician, who sent her into the hospital.

From the Medical Service, Receiving Hospital, and The Department of Medicine, Wayne University, College of Medicine, Detroit, Michigan.
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The *past history* and *family history* were not contributory. The patient had never had rheumatism, joint pains, growing pains, frequent nosebleeds, sore throats, or chorea, and no physician had ever reported a heart murmur.

Physical examination revealed a well-developed but critically ill colored girl who was dehydrated, irrational, and resistive. The temperature was 103.6° F, the pulse rate, 150, the respiratory rate, 28, and the blood pressure, 110/60.

The pupils reacted to light. In the conjunctival sacs there were numerous white-centered petechiae, both discrete and coalescing. Numerous hemorrhages, some with white centers, were present in both retinae. The optic discs were hyperemic, with indistinct margins and loss of cupping.

Scattered over the mucous membrane of the mouth, particularly on the palate, were more petechiae, many with white centers. The tongue was dry and coated, and the breath foul.

The neck was stiff, and the Kernig and Brudzinski tests were positive. The tendon reflexes were hyperactive, but equal, and ankle clonus was elicited. The Babinski reflex was present on the right.

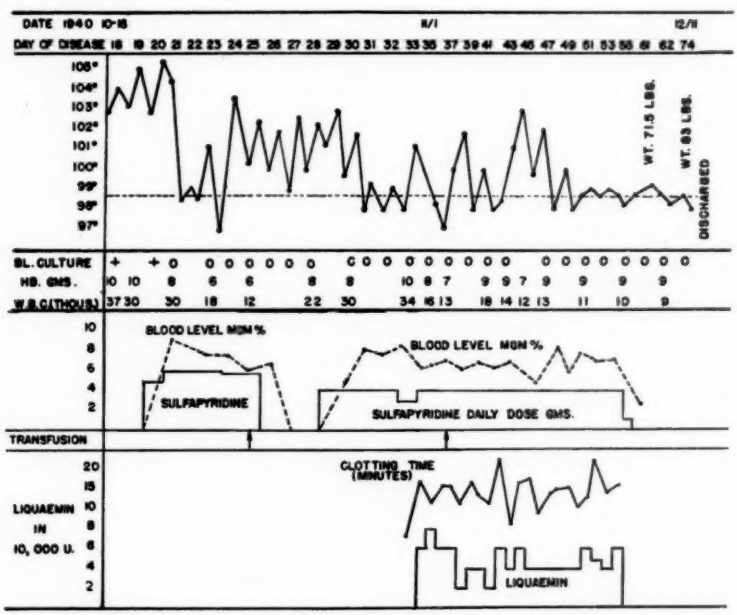

Fig. 1.—Chart illustrating course and treatment in case of *Micrococcus pharyngis siccus* endocarditis; described in text.

The lungs were normal.

The heart was of normal size; it was rapid and regular, and there was a rough systolic murmur over the entire precordium, loudest at the apex, and transmitted toward the axilla. No diastolic murmur was heard.

The abdomen was held voluntarily rigid during the examination, but there appeared to be some tenderness in the left upper quadrant beneath the costal margin. The spleen and liver were not felt.

A splinter hemorrhage was present under the fingernail of the left index finger. There was no clubbing.

Laboratory examination on admission showed a slight trace of albumin and 5 leucocytes per microscopic field in the urine. The leucocyte count was 37,200, with

92 per cent neutrophiles; the hemoglobin was 10 Gm. The blood Kline reaction was negative. On lumbar puncture, the initial pressure was 260 mm. of water. The spinal fluid was turbid, and contained a slight trace of globulin. The spinal fluid cell count showed 265 leucocytes, of which 95 per cent were neutrophiles; the Kline reaction was positive, and the dextrose content was 76 mg. per cent. No organisms were found on direct smear of the sediment, and culture was negative. Roentgenograms of the chest and paranasal sinuses were negative.

Bacteriologic Studies.—Blood cultures which were taken on the day of admission and two days later yielded a Gram-negative, bean-shaped diplococcus after about forty-eight hours' incubation. On blood agar the colonies appeared dry and grayish, and crumbled when removed. Agglutination tests with antimeningococcus serum were negative. Spontaneous agglutination occurred in physiologic saline solution. In fermentation tests, the organisms produced acid in dextrose, levulose, maltose, and sucrose, with no reaction in lactose, galactose, inulin, mannitol, and dulcitol. Because of these observations the organism was identified as *Micrococcus pharyngis siccus* in our laboratories, and this identification was confirmed by the laboratories of the Michigan State Health Department.

Course and treatment are charted in Fig. 1.

Sulfapyridine was begun on the second hospital day with an initial dose of 5 Gm. This drug was administered thereafter in doses of 4 to 6 Gm. daily from October 20 to November 22, save for three days when it was stopped because of a mistaken fear that it might be playing a role in the patient's rapidly increasing anemia. One-sixth of the daily dose (0.6 to 1.0 Gm.) was given every four hours, day and night. The blood level was maintained between 4.6 and 9.6 mg. per 100 c.c. during this thirty-three-day period. On the day after the first administration of sulfapyridine the blood cultures became negative, and they remained negative thereafter.* On the second day, the temperature fell to normal, but, after a chill, it became septic again within thirty-six hours.

The patient continued critically ill, and had a rapidly increasing anemia, so that transfusion was required. Almost every day new hemorrhages and white-centered petechiae appeared in the conjunctivae, retinae, or mucous membranes. One day a transient paralysis of the left external rectus oculi was demonstrated; there were two sudden attacks of left upper quadrant pain, associated with vomiting, and occasionally the urine showed erythrocytes. The apical systolic murmur became harsher. The electrocardiogram, which was normal on admission, showed transient inversion of the T wave in Lead I and transient flattening of the T wave in Lead IV-F. The patient's neck remained stiff, and another lumbar puncture showed pleocytosis, increased globulin, and a positive Kline reaction.

On November 1, the thirty-third day of her illness, and eleven days after sulfapyridine was begun, a supply of heparin was obtained, and an initial dose of 20,000 units of Liquaemin† was given intravenously. From November 1 until November 21, in order to maintain the coagulation time at about fifteen minutes by Lee and White's three-tube technique, 20,000 to 80,000 units of heparin, diluted with saline, were given intravenously daily. The average daily dose was about 40,000 units. Sulfapyridine was continued.

During two weeks of this combined therapy, the patient continued acutely ill. New petechiae were noted on November 5, 8, and 13. On the fifteenth day of combined treatment, she began to improve; her neck became less stiff, her headache disappeared, she became cooperative, and her temperature fell to normal. Seven days later, after three weeks of combined heparin-sulfapyridine therapy, medication was discontinued. Further recovery was uneventful.

*At this time, sodium para-aminobenzoate was not used in our blood-culture media.
†Liquaemin, a brand of heparin, was kindly supplied by the Hoffman-LaRoche Co.

TABLE I

PRINCIPAL CLINICAL FEATURES IN FIVE CASES OF *Micrococcus pharyngis siccus* ENDOCARDITIS

	AGE	COLOR	SEX	ONSET	PREVIOUS HEART DISEASE	HEART SIZE	HEART MURMURS	EMBOLIC MANIFESTATIONS				BLOOD CULTURE	LEUCOCYTE COUNT	DURATION ILLNESS (DAYS)
								PETECHIAE	MENINGEAL (SPINAL FLUID)	PALPABLE SPLEEN	HEMATURIA			
Schultz[1] (1918)	25	W	M	Sudden, with headache, fever, generalized aching	None	Normal	Rough, apical systolic, transmitted to axilla	Skin, mucous membranes, serosal surfaces	Irrational. C.S.F.: "pus and globulin"	Yes (about 500 Gm.)	Occasional	2 pos.	18,000 to 19,200	18*
Graef, et al.[2] (1932)	27	W	M	Sudden, with cramping lower abdominal pain, painful fingers and toes	Rheumatic, with mitral stenosis and insufficiency and aortic insuff.	Enlarged (945 Gm.)	Systolic and diastolic murmurs at both apex and base	Skin, mucous membranes, serosal surfaces, 2 Osler nodes	None	No (690 Gm.)	RBC increase in Addis count	1 pos.	Not reported	20*
Goldstein[3] (1934)	21	W	F	Sudden, with headache, chills and fever, generalized aching	Rheumatic, with mitral stenosis	Normal (300 Gm.)	Diastolic rumble at apex	Skin over chest	Stiff neck C.S.F.: 450 WBC, 98% PMN's Culture +	No (350 Gm.)	None	1 pos.	26,000	14*
Shiling[4] (1939)	26	W	M	Chills and fever for six weeks	None	Normal (350 Gm.)	Rough, apical systolic, transmitted to axilla	None; embolic occlusion of right brachial and femoral arteries	None	No (20[illegible] Gm.)	Frequent	"Many" pos.	16,000	91*
H. J. (New case)	14	B	F	Sudden, with headache, fever, blurred vision	None known	Normal (x-ray)	Rough, apical systolic, transmitted to axilla	Mucous membranes, retinae, skin	Stiff neck; Kernig + C.S.F.: 265 WBC, 95% PMN's Culture C	No	Occasional	2 pos.	29,000 to 37,200	49

*Illness terminated in death. Diagnosis proved by post-mortem examination.

She has remained well for one year. Examination on Nov. 14, 1941, revealed a well-developed and well-nourished girl who was apparently in good health. The temperature was 98° F., the pulse rate, 80, the respiratory rate, 20, the blood pressure, 118/80, and the weight, 103 pounds (a gain of 32 pounds during the year). Vision was 20/40 O.D., and 20/100 O.S.; this was correctible to 20/30 in both eyes. There was a whitish macular lesion in the right eye which had fairly sharply defined edges, and several small pigmented spots were seen about the macula of the left eye. Several small pigmented areas were also present on the soft palate. The heart was of normal size, but, roentgenographically, there was a slight increase in the left auricular curve. At the apex there was a rough systolic murmur, transmitted to the axilla, but no diastolic murmur was heard. The pulmonic second sound was accentuated and split. Neurologic examination was negative. Laboratory studies, including a blood culture and an electrocardiogram, showed nothing abnormal.

DISCUSSION

A review of all the reported cases of *Micrococcus pharyngis siccus* endocarditis is of some interest (Table I). The patients' ages ranged from 14 to 27 years. There were three males and two females. The onset of the disease was uniformly sudden, with headaches, chills, fever, and general malaise. Other symptoms depended upon the areas affected by emboli. In two instances, the site of the cardiac lesion was an otherwise normal mitral valve; in two, valves previously damaged by rheumatism were affected. All of the patients had rough cardiac murmurs, all had striking embolic manifestations, namely, petechiae, splinter hemorrhages under the nails, splenic infarcts, and renal infarcts, and three had meningeal involvement. All had a considerable leucocytosis, ranging from 16,000 to 37,000. The course of the illness was acute in three cases, in which death occurred on the fourteenth, eighteenth, and twentieth day, respectively, after onset. One patient lived thirteen weeks, and one, with meningeal involvement, who was treated with heparin and sulfapyridine, is apparently cured.

SUMMARY

A case of *Micrococcus pharyngis siccus* endocarditis is reported. This patient, who was acutely ill, and had meningeal involvement, multiple white-centered petechiae, occasional hematuria, and changing cardiac murmur, was treated with heparin and sulfapyridine, and recovered; she has remained well for one year.

Four other previously reported cases are reviewed.

ADDENDUM

The patient was in good health when re-examined in February, 1943. The cardiac signs were similar to those of Nov. 14, 1941.

REFERENCES

1. Schultz, Oscar T.: Acute Vegetative Endocarditis With Multiple Secondary Foci of Involvement Due to Micrococcus Pharyngitidis Siccae, J. A. M. A. 71: 1739, 1918.

2. Graef, I., De La Chapelle, C. E., and Vance, M. C.: Micrococcus Pharyngis Siccus Endocarditis, Am. J. Path. **8**: 347, 1932.
3. Goldstein, J. D.: Endocarditis Due to a Neisseria Pharyngis Organism, Am. J. M. Sc. **187**: 672, 1934.
4. Shiling, M. S.: Bacteriology of Endocarditis With Report of Two Unusual Cases, Ann. Int. Med. **13**: 476, 1939.
5. Wilson, G. S., and Smith, M. M.: Observations on Gram-Negative Cocci of the Nasopharynx With Description of Neisseria Pharyngis, J. Path. & Bact. **31**: 477, 1928.
6. Endres, G.: Der Mikrococcus Catarrhalis als Erreger einer Sepsis mit Endokarditis und Nephritis, München. med. Wchnschr. **72**: 723, 1925.
7. Kammerer, H., and Wegner, R. N.: Zur Aetiologie der Endokarditis lenta. Micrococcus flavus als Erreger, München. med. Wchnschr. **61**: 588, 1914.
8. Connaughton, F. W., and Rountree, P. M.: A Fatal Case of Infective Endocarditis Due to Neisseria Flava, M. J. Australia **2**: 138, 1939.
9. Coulter, C. B.: Gram-Negative Coccus Causing Fatal Endocarditis, Proc. N. York Path. Soc. **15**: 7, 1915.
10. Dammin, G. J.: Subacute Bacterial Endocarditis Caused by a Hitherto Undescribed Gram-Negative Coccus, Ann. Int. Med. **15**: 756, 1941.

Correspondence

To the Editor:

Our attention has just been called to the article by Patterson, Clark, and Levy, entitled "A Comparison of Electrocardiographic Changes Observed During the Anoxemia Test on Normal Persons and on Patients With Coronary Sclerosis," which appeared in the American Heart Journal, June, 1942, p. 837, and to the appended criticism of a paper by Burnett, Nims, and Josephson on the same subject in an earlier issue of the same journal. We have followed closely the work of the Colorado group, and, in our opinion, an analysis of the various articles published by Levy and his coworkers will support the unfavorable view of this test taken by Burnett and his group.

The method followed by Levy in the development of his criteria has evidently consisted of subjecting a group of persons who are normal with respect to their coronary circulation to the anoxemia test, and regarding all of the responses encountered as negative. Through the device of repeatedly revising their previously published electrocardiographic criteria for coronary inadequacy, they are now able to present data which show that all normal persons in their series exhibit a negative response. But this otherwise desirable feature of their test has been obtained at the expense of very largely destroying its ability to uncover hidden or subclinical coronary insufficiency, and of seriously diminishing the percentage of abnormal persons who respond with a positive reaction. Indeed, in their latest paper, only 49 per cent of the patients on whom the Levy group had made the clinical diagnosis of coronary sclerosis were positive reactors. Under these conditions, it seems pertinent to ask how much additional information a clinician may expect to get from the Levy test, in as much as the criteria make it unlikely that subclinical coronary insufficiency will be revealed, and, further, will, as like as not, provide a false negative response when the clinical observations point clearly to coronary sclerosis. On the other hand, any attempt to increase the percentage of positive reactors among the abnormal subjects by increasing somewhat the anoxemic stress will result, as the Burnett group have shown, in a substantial number of false positive reactors among the normal subjects.

The present unsatisfactory state of the Levy test is, in our opinion, due largely to two uncontrolled factors. The test, as now employed, is apparently not a direct measure of the status of the coronary circulation, but rather of myocardial anoxemia. The development of myocardial anoxemia under stress, however, is the net result of interaction between the coronary circulation and a complex of compensatory re-

actions. A person with a normal coronary circulation may thus react as a false positive because of a deficiency in these compensatory reactions, or, conversely, unusually efficient compensatory reactions may produce a false negative reaction in a person who has a moderate degree of coronary insufficiency. In other words, the degree of myocardial anoxemia, and, hence, the electrocardiographic response, does not necessarily reflect the condition of the coronary vessels. Another unfortunate feature of the Levy test is the fact that the criteria are based primarily upon the clinical diagnosis. As is well known, the clinical diagnosis of coronary sufficiency or insufficiency is uncertain. In fact, it was this uncertainty which led the Levy group to attempt the development of a test. As long as the present criteria are used, therefore, the Levy test can hardly be expected to add much to the accuracy of clinical diagnosis. The conclusion seems justified that some more secure foundation for the criteria must be found. Perhaps this will require the laborious correlation of the results of repeated tests with numerous and prolonged clinical observations, together with an analysis of the state of the vessels post mortem. A tremendous task!

Another important point at which we are in disagreement with the Levy group is the question of safety. These workers have, themselves, reported three instances of pulmonary edema and one of shock during the course of anoxemic stress. Although it is now recommended that no one should be subjected to the test twice in twenty-four hours, does not their own experience indicate that there is a definite hazard?

These criticisms of the Levy test are not made without a due appreciation of the very great difficulties inherent in the task which they have undertaken. It is rather our wish to give expression to our belief that the test, as yet, has not been developed sufficiently to warrant recommending its general adoption by the profession at large.

RICHARD W. WHITEHEAD
WILLIAM B. DRAPER
Denver, Colo.

TO THE EDITOR:

With the final conclusion of Whitehead and Draper I am in complete agreement, namely, that the time has not come when the anoxemia test should be recommended for general use. It certainly should not be employed by those who do not understand the principles upon which it is based and who are unable to carry out the directions which have been given for its performance.

The answers to most of the questions raised are to be found in papers published by my collaborators and myself, as well as in the addendum to the article which appeared in the AMERICAN HEART JOURNAL for June, 1942, p. 837. For the sake of clarity, I will recapitulate, and also cite some of the experiences of others who have used this procedure.

1. Criteria for the normal response obviously must be obtained from persons who present no clinical evidence of cardiac disease. Such normals do not die within a short time, so that the heart cannot be examined directly.

2. The test was electrocardiographically positive in 49 per cent of 157 cases of coronary sclerosis, and furnished presumptive evidence of coronary insufficiency, by the occurrence of pain, in another 20 per cent. It was thus helpful in the recognition of a diminished coronary reserve in 69 per cent. The importance of the occurrence of pain during the test has been fully discussed (J. A. M. A. **117**: 2113, 1941). Gilbert and his associates have used this method of induced anoxemia to study the effects of various drugs upon patients with angina of effort, depending solely upon the appearance of pain as an end point (references in paper cited above).

3. Individual case histories have been given in detail to indicate how the test may aid in diagnosis in doubtful cases. In a small number, postmortem examination has confirmed the results of the test. Serial observations over a period of years have already been reported.

4. Neither Burnett nor his colleagues are in a position to speak of the safety of the test, or, rather, of its dangers. They worked with a 10 per cent oxygen mixture at an elevation of 5,000 feet, which means that the patients actually breathed the equivalent of an 8 per cent mixture. In addition, in at least six cases, through error, Burnett used a mixture containing 8.6 per cent, so that these subjects inhaled about 7 per cent oxygen. As previously stated, because of the conditions of the Denver experiments, the results are not comparable to ours, and the conclusions drawn do not apply to the anoxemia test which we have described.

5. In the earlier period of our work several unpleasant reactions occurred. The test has now been made in our laboratory almost 2,000 times. We have advised that three precautions be observed. Only the first of these is mentioned by Whitehead and Draper, namely, that the test should not be performed more than once in twenty-four hours. In addition, we have urged that it should not be carried out in the presence of congestive heart failure or within four months of known cardiac infarction. If these directions are followed, serious reactions may be avoided.

6. The electrocardiographic response does not necessarily reflect the condition of the coronary arteries; we have specifically stated that "it yields no information as to the nature or extent of the pathologic lesions in the heart." But it does serve as an index of the coronary reserve, and, hence, of the adequacy of the coronary blood flow. As in all functional tests, there must be a significant diminution in reserve before a positive result is obtained.

A number of reports on the use of the anoxemia test have been made. Among them are the following:

Dr. Arlie R. Barnes, Mayo Clinic, Rochester, Minn. (Proc. Staff Meet., Mayo Clin. **17**: 316, 1942). The test was carried out on a patient "who was thought to have coronary sclerosis and who presented atypical symptoms of angina pectoris." After describing the changes observed in the electrocardiograms, which are reproduced, Barnes states: "I consider, therefore, that these changes are of sufficient degree and of a quality to confirm strongly the clinical suspicion that this patient had coronary insufficiency. On comparing the tracings before and during anoxia in a similar case in which the same question arose, depressions of the S-T segments were noted in Leads I, II, and IV-R. There seems little doubt that such changes are indicative of severe coronary insufficiency."

Dr. Harold J. Stewart, New York City (Letter). "We have been using your anoxemia test for fifteen months or so in my Sub-Department of Cardiology at the New York Hospital and Cornell University Medical College. We wished to accumulate data and form an impression from our own experience about the value of the test. We have been careful in adhering to the methods which you have devised and your technique. For six months we were running a fair number of tests, but in the last six months, because of staff shortage, I have had to limit the number to those requested rather than seeking cases to do. We have run seventy-five tests so far.

"1. We have had no difficulties in doing the test and no untoward effects have been encountered. We have kept in mind those cases in which you have advised against its use and the reasons for discontinuing a test.

"2. We did the test first in a certain number of normal individuals to get the feel of the test, setting of routine, etc.

"3. We have used your criteria in analyzing the results.

"4. We have done the test in certain types of patients. Our results have not been analyzed, but I have the following impressions:

"a. In those in whom clinically the symptoms appeared to be angina in order to see how the correlation fitted in them, it seems that either significant electrocardiographic changes or pain typical of their spontaneous attacks or both may occur with breathing of low O_2.

"b. Those with unusual distribution or occurrence of pain in which the question of angina could not be decided clinically, in which there might or might not be any electrocardiographic changes indicating coronary artery changes, and in which objective help was needed: In about half of these the test was positive and in about half negative.

"c. Those who did not from history, etc., appear to have angina and the facts in the examination and the laboratory data did not point to cardiac damage, but who thought they had angina: In most of these the test has been negative.

"I think that it is a useful test, and as my experience with it increases, I get more confidence in how to accept the results. I still want to see

the patient myself and make the clinical estimate of the pain and then see how it links up with the test. If an objective test parallels the clinical findings frequently enough, both in a negative and a positive way (i.e., typical angina and normals) it seems justifiable to go from the positive or negative test to the clinical interpretation, and as time goes on and more of the cases come to autopsy, the basis will be more clearly established, as you all too well emphasize. It may take putting together the experience of many investigators over years to make this latter correlation. I think you have been extremely careful in your claims for the test and have not stepped beyond the bounds of the content of your data in your own estimate of it."

Dr. Harold Feil, Lakeside Hospital, Cleveland, Ohio (Letter). "My results with the anoxemia test have been very satisfactory, and judging from clinical criteria there were no false positives. In one case the chest lead was more strongly positive than the exercise test. It is a diagnostic help in border-line cases, and parallels much the changes in the exercise test."

Dr. Nelson G. Russell, University of Buffalo, Buffalo, N. Y. (Letter). Dr. Russell kindly sent me full clinical notes and the autopsy protocol of a man, 51 years old, who gave a history of distress in the chest on exertion which came on after walking three or four blocks. The electrocardiogram showed no definite abnormality. The anoxemia test was positive, and pain appeared six minutes after the inhalation of 10 per cent oxygen was begun. The patient died suddenly one year and eleven months after the test was made. Examination of the heart at autopsy showed no cardiac enlargement. There was advanced atherosclerosis of all of the coronary arteries. The left was almost entirely occluded at its exit from the aorta, and the narrowed lumen contained a recent clot. The anterior descending branch was completely filled with an older, organized thrombus. The circumflex branch of the left coronary showed a thickened wall and moderate narrowing of its lumen. The right coronary was diffusely atherosclerotic, but its lumen was patent. No recent infarcts were present.

S. A. Thompon and M. J. Raisbeck, New York City (Ann. Int. Med. **16**: 495, 1942). These observers used induced anoxemia in studying patients prior to cardio-pericardiopexy. They describe the criteria of a positive test, and state: "We have considered such changes as evidence of a subnormal coronary blood supply." The electrocardiograms illustrating the test in three of their patients are published. They add: "In no cases have we observed the development of alarming symptoms or more than transient distress."

It is our hope that further studies will extend these observations and furnish additional evidence of the usefulness of the method.

ROBERT L. LEVY
New York, N. Y.

Abstracts and Reviews

Selected Abstracts

Kiely, W. F., Hamilton, S. L., and Gellhorn, E.: The Influence of Hemorrhage on Skeletal Muscle Tone. Am. J. Physiol. **137:** 251, 1942.

Hemorrhage leads in unanesthetized, decerebrate dogs to a rise in muscle tone which is reversed on reinfusion of the blood.

Adrenalin raises blood pressure and muscle tone but ephedrine is without effect on the muscle tone in concentrations which have a decided pressor effect.

Hemorrhage causes a rise in muscle tone even when a fall in blood pressure is prevented by simultaneous injection of ephedrine.

Bilateral denervation of the carotid sinus area does not prevent the rise in muscle tone during hemorrhage.

AUTHORS.

Calabresi, M., and Geiger, A. J.: Potential Changes in Injured Cardiac Muscle. Am. J. Physiol. **137:** 440, 1942.

Evidence obtained both electrographically and by means of a suitable microvoltmeter indicates that the surface of an area of injury in the beating heart is the site of important changes in electrical activity during systole, and that the monophasic electrogram obtained from the injured heart results predominantly from potential changes at the electrode over the injured area. The authors' observations therefore stand in opposition to the traditional view in this regard, and they confirm the stand recently taken by several others.

AUTHORS.

Shuler, R. H., Ensor, C., Gunning, R. E., Moss, W. G., Johnson, V.: The Differential Effects of Respiration on the Left and Right Ventricles. Am. J. Physiol. **137:** 620, 1942.

In dogs anesthetized by sodium barbital, direct cardiac volume changes were measured by means of an oncometer during normal breathing, with the ventricles exposed to intrathoracic pressure changes. During inspiration there was an increase in total diastolic size and stroke volume of the two ventricles. This confirms the findings of Boyd and Patras (1941).

Systemic arterial pressure decreased during inspiration in spite of increased total cardiac output during the same phase of respiration.

Under sodium barbital anesthesia, a portion of the ventral chest wall was removed, the heart exposed, and paper markers affixed to the heart so as to outline each ventricle. A window was sealed into the ventral chest opening, normal respiration was reinstated, and motion pictures were taken of the heart. Successive single frames were projected, the area of each ventricle measured in each frame, and these areas plotted together with simultaneous intrathoracic and carotid pressures. The right ventricle showed increased diastolic size and stroke volume during inspiration, while the same measurements on the left ventricle decreased; the reverse was true during expiration.

The increased diastolic size and stroke of the right ventricle during inspiration suggest that more blood is pumped into the lungs during that phase, while the decreased diastolic size and stroke of the left ventricle indicate that the blood is withheld from the left side of the heart until the onset of expiration.

Systemic arterial blood pressure measurements on trained, unanesthetized dogs showed but slight reduction of respiratory influences on blood pressure when intrathoracic pressure influences were eliminated by the use of a differential manometer. These reductions are equivalent to simultaneous intrathoracic pressures, but are not sufficient to eliminate respiratory fluctuations in blood pressure.

The main factor responsible for the arterial blood pressure fluctuations of respiration is the changing output of the left ventricle. A sinus arrhythmia and direct influences of intrathoracic pressures may modify somewhat these blood pressure changes.

Each ventricle responds independently in accordance with the Starling principle, regardless of the diastolic size of the other ventricle.

AUTHORS.

Woodbury, R. A., and Robertson, G. G.: The One Ventricle Pump and the Pulmonary Arterial Pressure of the Turtle: The Influence of Artificial Acceleration of the Heart, Changes in Temperature, Hemorrhage and Epinephrine. Am. J. Physiol. **137**: 628, 1942.

The right and left aortic pressure pulses of turtles are synchronous and show equal pressures. Blood flow and the systolic pressure rise occurs slightly earlier in the pulmonary artery than in the aortas. During the last part of systole the pulmonary pressure becomes 2 or more mm. Hg below that in the aortas. During diastole the pulmonary pressure descends more rapidly and to a lower value than that in the aortas.

No evidence was obtained that the ventricle retains any significant residual volume of blood at the end of the ejection period. The cardiac output in turtles is increased by an increased heart rate and/or an increased diastolic filling of the ventricle.

Cooling or warming the turtle respectively lowers or elevates the pulmonary systolic and diastolic pressure. At body temperatures near 0° C., diastole is excessively prolonged. This is vagal in origin.

The presence of only one ventricle enables the turtle to regulate effectively the distribution of blood flow between the systemic and pulmonary areas. If the need arises (after hemorrhage) blood flow can be diverted into the systemic vessels by closing off the orifice of the pulmonary artery during the greater part of systole and by reducing the size of the pulmonary arterial reservoir.

Epinephrine HCl administered intravascularly increased the peripheral resistance of the systemic vessels, increased the muscle tone of the great pulmonary arteries, but gave no evidence of any effect upon the peripheral resistance of the pulmonary circulation.

AUTHORS.

Warren, J. V., Walter, C. W., Romano, J., and Stead, E. A., Jr.: Blood Flow in the Hand and Forearm After Paravertebral Block of the Sympathetic Ganglia. Evidence Against Sympathetic Vasodilator Nerves in the Extremities of Man. J. Clin. Investigation. **21**: 665, 1942.

On two occasions, the sympathetic ganglia supplying the right upper extremity of a normal subject were injected with novocain by the paravertebral route. The blood flow in the hand and forearm was measured before, during, and after the anesthetization.

Complete absence of any vasomotor activity in response to sensory stimuli or deep inspiration indicated complete paralysis of the sympathetic ganglia supplying the right hand. The sympathetic paralysis produced a striking increase in blood flow. After the effect of novocain had passed away the right hand was immersed in water at a temperature of 43° C. Local heat produced the same increase in blood flow in the right hand as had sympathetic paralysis.

The fact that complete blocking of sympathetic ganglia produces full vaso dilatation in the hand demonstrates that inhibition of sympathetic activity is sufficient to explain the vasodilatation which occurs in the hand when the body is heated. There is no necessity for postulating that the sympathetic nerves to the hand contain vasodilator fibers.

In the forearm, paravertebral novocainization of the sympathetic ganglia caused a six-fold increase in blood flow. A similar increase in blood flow was produced by immersing the forearm in hot water (46° C.). This indicates that removal of all sympathetic impulses to the vessels of the forearm produces as great a rise in blood flow as does heating the part. Inhibition of vasoconstriction adequately explains the increase in blood flow which occurs when the body is heated, and there is no need to assume that the sympathetic nerves to the forearm contain vasodilator fibers.

The fact that neither heating the forearm nor injection of the sympathetic ganglia with novocain produces maximal dilatation in the forearm indicates that many of the vessels of the forearm are not under control of the sympathetic nervous system. It is suggested that the vessels of the skin of the forearm are under the control of the sympathetic nervous system, and that those of the muscle are not.

AUTHORS.

Swank, R. L., and Bessey, O. A.: Production and Study of Cardiac Failure in Thiamine-Deficient Pigeons. Arch. Int. Med. 70: 763, 1942.

A chronic deficiency of thiamine without starvation will produce signs of cardiac failure in pigeons.

This is preceded and accompanied by tachycardia and electrocardiographic abnormalities.

Necrosis of myocardial fibers with inflammatory cell infiltration occurs frequently, although late, in thiamine-deficient pigeons.

The electrocardiographic abnormalities and evidences of cardiac failure in thiamine-deficient pigeons are accompanied by marked decrease in the cocarboxylase content of the heart muscle.

The electrocardiographic abnormalities and the evidence of cardiac failure, if not too severe, respond immediately to treatment either with thiamine hydrochloride or cocarboxylase.

Starvation alone or during thiamine deficiency produces bradycardia and frequently variable heart block in pigeons.

The methods and mechanism by which tachycardia and evidences of cardiac failure are produced in thiamine deficiency are presented and discussed. It is suggested that the tachycardia is due to vasodilatation, which is caused by the local accumulation of intermediate products of carbohydrate metabolism. This also facilitates transudation of fluid from blood vessels to form hydropericardium and other evidences of cardiac failure. In addition, thiamine deficiency impairs the function of the heart, increases the tendency to extravascular fluid collections and results in terminal cardiac standstill. It seems probable that thiamine deficiency, in the absence of peripheral vasodilatation, causes bradycardia, but unfortunately most experiments involving such deficiency have been complicated by marked starvation, which also is known to cause bradycardia.

AUTHORS.

Zeek, P. M.: Heart Weight. I. The Weight of the Normal Human Heart. Arch. Path. 34: 820, 1942.

Statistical analysis of the weights of hearts from 926 adult bodies in which was found no clinical or pathologic evidence of heart disease or of any commonly recognized cause of myocardial hypertrophy revealed the following factors to have an effect on heart weight: sex, body length and state of body nourishment. No effect of age or race on heart weight was demonstrated.

In relatively normally nourished males the weight in grams of a normal heart was found to be 1.9 B. L. -2.1±40, B. L. being the body length in centimeters. The normal heart weight in normally nourished females was found to be 1.78 B. L. -21.58±30. Since emaciation and obesity are parts of pathologic processes, the variations in heart weights found to be associated with these conditions were considered departures from normal. Therefore, bodies presenting these conditions were not included in the series used for the determination of standards for normal heart weight. These standards based on body length were found to be more accurate and more useful than the commonly employed standards related to body weight.

AUTHOR.

Schleser, I. H., and Langendorf: The Significance of the So-Called P-Pulmonale Pattern in the Electrocardiogram. Am. J. M. Sc. 204: 725, 1942.

The P-pulmonale pattern is not pathognomonic of chronic pulmonary disease, since it occurs in its absence, as it appears in a variety of other conditions.

P-pulmonale in association with low "voltage" in the limb leads or with right ventricular preponderance represents the characteristic electrocardiogram of chronic cor pulmonale.

It is of diagnostic importance to distinguish the P-pulmonale pattern from that seen in rheumatic mitral stenosis. The P-wave pattern can be used as a diagnostic hint in determining the cause of right ventricular preponderance if both are found in the same record.

Further anatomic and roentgen ray correlation studies are necessary to establish definitely whether P-pulmonale is due to altered position, increased strain on, or hypertrophy of the right auricle.

AUTHORS.

Burchell, H. B.: Observations on Additional Instances of a Supernormal Phase in the Human Heart. J. Lab. & Clin. Med. 28: 7, 1942.

The presence of the supernormal period in the human heart has been used to explain cases of interference dissociation in which the auricles are beating more rapidly than the ventricles, cases of paroxysmal heart block in which cessation and resumption of auriculoventricular conduction have a phasic dependency on the immediately preceding electrical events and cases of possible parasystolic rhythm. An example is given of each of the first two types of mechanism which are best explained by the existence of a supernormal period in excitability of the conduction tissues. Case 2 is considered of some importance, as it is another instance of the undoubtedly rare cases in which the supernormal period has played a role in the maintenance of normal sinus rhythm. Following establishment of complete block, the patient has remained in relatively good health for two years.

AUTHOR.

Miller, J. R., and Dent, R. F.: A New Hypothesis of the Production of the T Wave in the Electrocardiogram Based on Electrokinetic Phenomena. J. Lab. & Clin. Med. **28**: 168, 1942.

The nature of the T wave in the electrocardiogram suggests that it is due to an electrokinetic cause and does not represent retreat electric disturbances. The structure of the heart with its capillary bed is such that contraction could produce streaming potentials of the order of magnitude of the T waves. Pressure perfusion of the heart showed this to be entirely possible. Constriction of the unresponsive heart likewise produced this phenomenon. In addition it is shown that the T wave corresponds in time to the increase in pressure in the left ventricle. These observations suggest that contraction of the heart with its resultant streaming potentials is responsible for the T wave in the electrocardiogram.

AUTHORS.

Richardson, J. S.: Chest Leads in Congenital and Acquired Dextrocardia. Brit. Heart J. **4**: 80, 1942.

Two cases of congenital dextrocardia with transposition of the viscera were found to have in chest leads, T waves that had deflections in the opposite direction from the normal.

In two cases of acquired dextrocardia, one had T waves in leads, taken from the right side of the chest, that resembled those of congenital dextrocardia in direction, but the other conformed to the tracing found in about 20 per cent of subjects with normally placed hearts.

AUTHOR.

Abbott, G. A., and Russek, H. I.: Calcareous Aortic Stenosis in a Case of Dextrocardia With Situs Inversus. Am. J. M. Sc. **204**: 516, 1942.

A case is presented in which calcareous aortic stenosis (rheumatic?) was found in a 43-year-old male with situs inversus. Electrocardiograms showed the effect of the conditions cited. There is no evidence of a similar case having been reported.

AUTHORS.

Abramson, D. I., Fierst, S. M., and Flachs, K.: Effect of Muscular Exercise Upon the Peripheral Circulation in Patients With Valvular Heart Disease. J. Clin. Investigation **21**: 747, 1942.

Using the venous occlusion plethysmographic method, the rate of resting peripheral blood flow and the circulatory response to exercise were studied in a series of 29 patients with insufficiency of the aortic semilunar valves, and in 16 subjects with mitral valvular disease.

The average circulation in the hand was found to be somewhat diminished in both series of patients as compared with that for the control series, while the readings in the forearm and leg in the majority of the cases fell within the normal range.

The post-exercise response of the blood vessels in the forearm to a specified amount of work was generally greater than that in the control group.

It was concluded that, in the majority of the patients with aortic insufficiency or mitral valvular disease, no evidence was found to indicate that excessive vasodilatation or vasoconstriction exists in the vessels of the forearm or leg.

On the basis of the results obtained with a period of exercise, it appears either that the compensatory circulatory mechanisms elicited by such a stimulus are not as effective as normal, that the work is performed with less efficiency, or possibly that both mechanisms are operating in this condition.

AUTHORS.

Cotton, T. F.: Some Aspects of Carditis. Brit. M. J. 2: 473, 1942.

Observations are made on the prognosis in carditis, based on the after-histories of two hundred boys, average age 11 years.

Rather more than one-half of the children with carditis are alive and slightly more than one-third are dead ten years after from four and one-half to six months' treatment in a special convalescent home. The large number of untraced cases prevents the author from concluding that the prognosis is more favorable when the stay in a convalescent home is increased from four and one-half to six months.

Rather less than half of those who die within ten years live longer than five years after treatment in a special convalescent home.

The death rate in children with mitral stenosis and aortic regurgitation is much higher than in those with mitral systolic murmurs, over a 10-year period.

Children with moderate or considerable enlargement of the heart are less likely to live ten years than those with slight or no enlargement.

AUTHOR.

Strassmann, G., and Goldstein, P.: Syphilis of the Aorta and Coronary Arteries. Arch. Path. 34: 745, 1942.

Sudden death caused by syphilitic aortitis associated with stenosis or occlusion of the orifice of one or both coronary arteries is fairly common. Syphilitic aortitis is often associated with arteriosclerosis of the coronary arteries. Seventeen of twenty-eight cases of sudden death caused by syphilitic aortitis with stenosis of the mouths of the coronary arteries investigated by the Office of the Chief Medical Examiner of the City of New York in Manhattan during the years 1940 and 1941 showed moderate or advanced coronary arteriosclerosis. A combination of syphilitic aortitis with syphilis of the coronary arteries distal to their orifices is, however, rare.

The case which the authors report showed a combination of syphilitic aortitis and syphilitic coronary arteritis. The aortitis produced stenosis of the orifices of both coronary arteries and the arteritis resulted in marked narrowing of the lumen of the main branches of both vessels. In combination, these two processes impaired the blood supply of the myocardium and were undoubtedly responsible for the sudden death.

AUTHORS.

Hamilton-Paterson, J. L., and Castleden, L. I. M.: Intracardiac Tumors. Brit. Heart J. 4: 103, 1942.

Three cases of intracardiac tumor are described, a sarcoma, a "pseudomyxoma," and an aneurysm, which produced signs and symptoms attributable to Ayerza's syndrome, mitral stenosis, and pulmonary stenosis respectively.

The origin of pseudomyxomata of the heart is discussed. It is suggested that they are not primarily neoplastic but are pedunculated thrombi as all their histological features may be reproduced in organizing blood clots.

A classification of heart tumors is suggested: Benign tumors resulting from organization of blood clot—pseudomyxomata; malignant tumors arising from any of the mesenchymal elements of the heart wall, the true sarcomata; and benign congenital tumors arising from developing myocardial elements, the congenital rhabdomyomata (dysontogenetic rhabdomyoma, hamartoma).

AUTHORS.

Solomon, C., Roberts, J. E., and Lisa, J. R.: The Heart in Uremia. Am. J. Path. **18:** 729, 1942.

The pathological findings in fifty hearts of patients dying in uremia are reported. No lesion was found which could be considered characteristic of the uremic state. In seven of eight cases with acute necrotizing arteriolitis of the kidneys, an unusual endothelial hyperplasia of the cardiac arterioles was present. In no other type of renal pathology was there any correlation with the cardiac changes. There was a definite relation between the presence of acute lesions of the myocardial fibers and the occurrence of clinical signs of cardiac dysfunction.

WILLIAMS.

Roth, G. M., and Sheard, C.: The Effect of Peripheral Vasodilatation on Vasoconstriction: Determinations Made on the Basis of Blood Pressure of Normal Subjects. Am. J. Physiol. **137:** 695, 1942.

In these twelve normal subjects, irrespective of the basal metabolic rate and irrespective of the existing generalized peripheral vasodilatation, the response to the vasoconstricting agent was not altered significantly.

AUTHORS.

Eichna, L. W., and Wilkins, R. W.: Capillary Blood Pressure in Man. Direct Measurements in the Digits During Induced Vasoconstriction. J. Clin. Investigation **21:** 697, 1942.

In the normal-sized digital capillaries of healthy subjects and of hypertensive patients, neurogenic vasoconstrictor stimuli brought about decreases in capillary blood pressure of from 5 per cent to 33 per cent.

Reflex vasodilatation in the digit, even when combined with local vasodilatation produced by histamine, failed to prevent the fall in capillary blood pressure which occurred in response to neurogenic vasoconstrictor stimuli.

The percentage variation in digital capillary blood pressure was considerably smaller than the percentage variation in digital blood flow which has been reported to occur during similarly induced vasoconstrictions.

In the abnormally large digital capillaries of patients with Raynaud's disease and scleroderma, neurogenic vasoconstrictions, and vasoconstrictions induced by the intravenous injection of epinephrin, were usually accompanied by decreases in capillary blood pressure.

After interruption of the sympathetic nervous pathways to the digits of patients with Raynaud's disease and scleroderma, neurogenic vasoconstrictor stimuli failed to induce in the sympathectomized digits either vasoconstriction or fall in capillary blood pressure. On the other hand, intravenously injected epinephrine continued to cause both vasoconstriction and fall in capillary blood pressures.

These observations have been interpreted as indicating (a) that although strong physiologic vasoconstriction mediated through sympathetic nervous pathways may be accompanied by a fall in digital capillary blood pressure, the fall is relatively slight; and (b) that the digital capillary blood pressure may remain at a relatively constant level during wide fluctuations in digital blood flow.

AUTHORS.

Schafer, P. W.: Body Fluid Changes in Neurogenic Hypertension and Total Paravertebral Sympathectomy. Proc. Soc. Exper. Biol. & Med. **49:** 327, 1942.

Changes in blood volume, plasma volume, hematocrit and red blood cell count have been studied in hypertensive dogs subjected to total paravertebral sympathectomy and in sympathectomized dogs subjected to the procedure used for production of hypertension. It was found that dogs subjected to modulator nerve

section developed marked hypertension and a markedly increased total blood volume apparently due to an increase in the cellular fraction of the blood. When these dogs were subjected to total paravertebral sympathectomy they regained approximately a normal total blood volume and their hypertension was markedly reduced; these changes were apparently due to a decrease in cells alone as the plasma volume remained unchanged. Normal dogs subjected to total paravertebral sympathectomy developed a slight hypotension and a slightly increased total blood volume due to an increase in the plasma fraction of the blood. When these sympathectomized dogs were subjected to modulator nerve section they developed a moderate hypertension not associated with any significant change in total blood volume, either in its cellular or plasma fraction.

WILLIAMS.

Kempf, G. F., and Page, I. H.: Production of Experimental Hypertension and the Indirect Determination of Systolic Arterial Pressure in Rats. J. Lab. & Clin. Med. 27: 1192, 1942.

Silk perinephritis and constriction of the renal artery by a silk thread both elicit arterial hypertension in rats of a degree sufficient for assay of renal antipressor extracts. The preparation of hypertensive rats by these methods is described.

The method of Williams, Harrison, and Grollman for measurement of systolic blood pressure has been modified to increase its effectiveness.

AUTHORS.

Neumann, C., Cohn, A. E., and Burch, G. E.: A Study of the Influence of the Character of an Examining Room on the Peripheral Blood Vessels of Normal, Hypertensive, and Senile Subjects. J. Clin. Investigation 21: 651, 1942.

Objective evidence supports the belief that the conditions under which physiological studies are carried out must be suitably arranged, not only to assure uniform temperature, humidity, and state of digestion, but also less tangible factors such as the patient's mental comfort and the degree of his relaxation. This was demonstrated by converting a "laboratory" into a conventional bedroom and by observing how the frequency of reaction on the part of peripheral blood vessels increased when sensory stimuli were applied at distant parts of the body. This observation was made not only in the case of groups of hypertensive and senile subjects but also in individual subjects studied under both types of environment. Conversely, in tense individuals, to be unable to relax in the atmosphere of a "laboratory" is evidence of the possible presence of an abnormal process.

AUTHORS.

Burch, G. E., Cohn, A. E., and Neumann, C.: Reactivity of Intact Blood Vessels of the Fingers and Toes to Sensory Stimuli in Normal Resting Adults, in Patients With Hypertension, and in Senile Subjects. J. Clin. Investigation 21: 655, 1942.

The mean reaction times in the tips of the fingers in normal (3.12) and in senile persons (3.86) differ from those in hypertensive patients (2.94), being more rapid in the hypertensive and slowest in the senile persons. In the tips of the toes, the general arrangement is the same, being fastest in hypertensive patients (3.24) and slowest in the senile (4.25). In the toes, the delay (beyond the fingers) is of the same order of magnitude in each of the three groups. This can be accounted for on the basis of the time required for the efferent impulses to traverse the additional length of post-ganglionic sympathetic fibers in order to reach the toes. The stimuli used were diffuse light, heat, cold, pin-prick, sudden loud noise (pistol-shot), and

electric shock. There was no significant difference in the normal group among the stimuli used in the reaction time or in any part of the total vascular response, such as time for the vasoconstriction to reach a maximum, degree of change in the volume of the pulse wave, time for recovery, and suddenness of response. It was not possible to group persons on the basis of their reactions to the stimuli.

The stimuli, light and bell, which were applied while subjects were alone were more satisfactory than those which, when applied, necessitated the presence of an observer. Psychological factors, often apparently very mild, influenced the responses significantly, which indicated the extreme importance of recognizing them during peripheral vascular studies on conscious human beings.

No correlation was found, provided a reaction to the stimulus occurred, between the reaction time and the state of the vascular bed of the part. The reaction time was essentially not affected by the fact that the vascular bed was already in a contracted or dilated state or was constricting or dilating when the stimulus was applied. This was not the case concerning the degree of change in volume of the vascular bed during the response. The more constricted the vascular bed at the time of stimulation, the less change in volume.

In general, the data strongly suggest that reaction time was more rapid, the vascular response occurred more suddenly and to a greater degree and was over more rapidly, in hypertensive than in normal subjects.

In the senile subjects, the reaction time was less rapid than normal and the vascular response occurred more slowly, to a less degree, and the recovery was much slower.

The reason for these differences in unknown. These differences can be owing to changes in the vessels themselves or in factors outside the vessels such as the nervous system or in chemical states which influence the vessels.

AUTHORS.

Di Palma, J. R., and Foster, F. I.: Sensitivity of the Smallest Cutaneous Blood Vessels: Quantitative Responses to Graded Mechanical Stimulation and to Local Ischemia in Arterial Hypertension, Arteriosclerosis, and Certain Allied Disorders. J. Clin. Investigation 21: 675, 1942.

The responses to graded mechanical stimulation, and to local ischemia of the smallest blood vessels of the skin of the ventral surface of the forearm, were quantitated in fifty patients with arterial hypertension twenty-five patients with arterial hypertension associated with arteriosclerosis, and twenty-three patients with arteriosclerosis. Also included in this study were eleven cases of malignant hypertension, and thirteen cases of hypertension associated with various types of nerve lesions, which influenced their capillary sensitivity. These results were compared to similar studies of a suitable control group of thirty-two subjects. The implications of the abnormal responses obtained were discussed. The following conclusions were reached.

In the group with arterial hypertension, it was demonstrated that the responses of the small dermal vessels, as quantitated in this study, are in no way significantly different from those of a comparable normal group.

No relationship was found between the severity of the hypertensive process, excluding the malignant phase, and the functional responses of the small cutaneous vessels. Many cases of very severe hypertension with diastolic blood pressures of over 130 mm. Hg. were studied, and showed normal capillary responses.

The conclusions for the purely hypertensive group apply as well to those patients with hypertension associated with ateriosclerosis, and with uncomplicated arteriosclerosis.

Of eleven patients with the malignant syndrome of hypertension, ten had small blood vessel responses which indicated greatly decreased sensitivity. This was especially evidenced, in five of these patients, by a complete inability of the small dermal vessels to respond by reactive hyperemia to local ischemia.

Thirteen patients with hypertension complicated by a nerve lesion, ranging from a cerebral vascular accident to Parkinson's disease, were found to have small cutaneous vessels as much as eighteen times more sensitive than the normal or hypertensive groups. Very irritable, small, dermal blood vessels may therefore exist even in the presence of arterial hypertension.

The above conclusions suggest that the humoral agent now believed responsible for arterial hypertension does not exert its influence upon the smallest blood vessels in the benign stages of the disease but may do so in the later malignant phase. If this is confirmed, the quantitative responses of the small dermal vessels might serve as a criterion of the extent of the vascular lesions in advancing hypertensive disease.

AUTHORS.

Katz, L. N., Shleser, I. H., Asher, R., and Perlow, S.: Prevention of Experimental Shock Following Venous Occlusion in the Dog by the Application of a Rigid Cast. Am. J. Physiol. **137:** 589, 1942.

In a series of thirteen dogs the application of a plaster cast for thirty-six hours to the lower extremities led to the survival of eleven animals following venous occlusion of the limb. Only one dog died in shock. This contrasts with the development of shock in thirteen out of fifteen dogs following this operation when no cast is applied, death occurring in three and one-half to twenty-one hours.

These results indicate that the cast by preventing the local accumulation of plasma fluid avoided the shock syndrome.

The local fluid accumulation which occurred following the removal of the cast developed at a slower rate than in the control series. The absence of untoward results in the period following removal of the cast suggests that for the shock syndrome to become established the loss of plasma fluids must occur at a rapid rate, a rate faster than compensating mechanisms can cope with.

This casting procedure appears to be applicable clinically for use in both civilian and military crush injuries.

AUTHORS.

Schecter, A. E., Cullen, M. L., and Freeman, N. E.: The Production of Shock by Trauma After Spinal Cord Transection. Am. J. Physiol. **137:** 710, 1942.

The spinal cord was transected between the first and second thoracic vertebrae in eight dogs. The animals were studied two or more days after recovery from this operation. The muscles of one hind leg were traumatized by 1,000 blows with a rubber hammer, and the bones of the extremity were fractured with a heavy metal bar. Blood loss into the area of injury was restricted by binding the extremity. The adequacy of circulation was determined by measurements of blood pressure, peripheral blood flow, cardiac output and oxygen content of mixed venous blood. Pathological changes characteristic of shock were found at post mortem. A reduction of blood volume and hemoconcentration occurred after trauma in the presence of a well-maintained circulation and in the absence of excessive blood loss into the injured extremities. These findings suggest the action of some factor capable of causing a reduction in blood volume not primarily due to excessive loss or to reduced circulation.

ROTH.

Bancker, E. A., Jr.: Coronary Thrombosis: Report of a Study of Fifty-Five Cases. J. M. A. Georgia **31**: 156, 1942.

In the fifty-five cases reported, posterior thrombosis outnumbered anterior thrombosis by one. The mortality rate was 38 per cent.

AUTHOR.

Waldman, S.: A Method for Rapid, Repeated, Approximate Determinations of the Transverse Diameter of the Heart. J. Lab. & Clin. Med. **28**: 201, 1942.

A simple method of immediate approximate measurement of the transverse diameter of the heart is described, obviating to a certain extent the use of orthodiagrams and teleoroentgenograms. Repeated studies in the same patient give excellent comparative results, and changes in the size of the heart are easily observed and recorded. Film is conserved, and time and expense are reduced to a minimum.

AUTHOR.

Leach, J. E., and Sugiura, K.: Late Effect of High Voltage Roentgen Rays on the Heart of Adult Rats. Am. J. Roentgenol. **48**: 81, 1942.

Doses of from 750 to 7,500 roentgens of 200 K.V. roentgen rays were given over the heart of adult rats. The animals were sacrificed at intervals of from four to fifteen months later and the hearts examined grossly and microscopically. These doses produced no demonstrable effects on the hearts. The fluid flow theory of Failla was applied to explain the relative resistance of the myocardium to roentgen irradiation.

WILLIAMS.

Wheeler, Sir W. I. de C.: Ligature of Innominate Artery for Right Subclavian Aneurysm: End-Result. Brit. M. J. **2**: 422, 1942.

Ligature of the innominate artery is not a difficult operation provided the exposure is adequate. Exploration, and the clearing of the deep surface of the manubrium sterni, are greatly facilitated by turning down the middle portion of the clavicle. In most cases this should be the first major step in the operation.

If ligature of the innominate is seen to be necessary a portion of the sternum should be divided and retracted upwards with the inner end of the clavicle. This can be accomplished without division of the first costal cartilage.

AUTHOR.

Westcott, F. H.: Social Aspect of Heart Disease in Industry. New York State J. Med. **42**: 955, 1942.

Illness accounts for 75 per cent of lost time in a large commercial organization, as compared to 25 per cent lost by reason of injuries. About 8 per cent of total time loss is due to cardiovascular disease.

The amount of time lost for cardiac disease is greatest in the case of unexamined and unselected employees and least in the case of those employed as group A risks.

The percentage of cardiacs losing time is smallest in the D group—those not covered by disability—and highest among the older employees entitled to all disability benefits.

Chronic myocarditis with decompensation and arteriosclerotic cardiovascular disease constitute at least 50 per cent of all cardiac disability.

By selective physical employment and a graded sick benefit plan, those employees liable to lose time because of heart disease other than from acute accidents, can be segregated and given gainful work of a type in which further damage to a diseased heart is avoided. Such a plan of employment eliminates the danger of setting up a social and economic inequality in the case of certain applicants.

AUTHOR.

Bondy, P. K., and Altschule, M. D.: The Action of Furmethide (Furfuryl-Trimethyl-Ammonium Iodid) on the Cardiovascular System in Man. Am. J. M. Sc. **204**: 334, 1942.

The reactions of 29 patients to the parasympathomimetic drug Furmethide (furfuryl-trimethyl-ammonium iodid) in parenteral doses of 3 to 20 mg., and in oral doses of 10 to 35 mg., were studied. Particular attention was paid to its effects on the cardiovascular system. Transient falls of systolic and diastolic blood pressures, tachycardia and rises of venous pressure occurred in patients receiving the drug parenterally. No such reactions occurred in patients receiving the drug orally. The side reactions include flush, sweating and urgency of urination. In the doses recommended for the treatment of atonic bladders (i.e., 3 to 5 mg. subcutaneously or 10 to 25 mg. orally) these reactions were not so marked as to make the patient uncomfortable.

The drug may safely be repeated after an hour when given subcutaneously, or after 4 hours when given orally.

Large doses of Furmethide should not be given parenterally to old patients or patients with known heart disease, as the tachycardia and fall in blood pressure may give rise to myocardial infarction. Very small doses should be used first in such patients, gradually increasing the dose after it has been shown that the smallest doses are without effect. The use of Furmethide by the oral route appears to be preferable in patients with heart disease.

Patients receiving Furmethide parenterally should be kept covered and in bed until the flush reaction has worn off, in order to guard against great losses of body heat during the sweating and vasomotor reactions.

AUTHORS.

Moia, B., and Quesada, R.: The Treatment of Arterial Hypertension by Thyocyanate. Rev. argent. de cardiol. **9**: 41, 1942.

Thirty patients with essential hypertension, with blood pressures over 200 mm. Hg systolic and 120 mm. Hg diastolic were used in this study. None of them were in the malignant phase or had congestive cardiac failure. After more than 4 years of treatment with usual therapeutic means, they received during 10 months, as exclusive treatment, potassium thyocyanate 0.30-0.60 gr. daily. The hematic concentration of the drug was explored weekly by the micro-method of Griffith and Lindauer, slightly modified.

The results obtained were good (group I) and 6 cases (20 per cent) with a decrease in blood pressure of 70-80 mm. Hg systolic and 20-25 diastolic; fairly good (group II) in 13 cases (43.3 per cent) with a decrease of 30-40 mm. Hg and 10-15 mm. Hg systolic and diastolic pressure respectively. Greater doses did not alter the results in this group even when levels higher than 10 mg. of potassium cyanate per cent were reached in the blood. In the other 19 patients (36.7 per cent) the results were bad (group III).

No relation was found between the condition of the eyegrounds and the results obtained. But it was found that patients in which the blood pressure was unstable responded better to treatment by thyocyanate: the results in these patients were more favorable and persistent.

All the patients of group I and some of group II were relieved of subjective symptoms, not so those of group III. Generally speaking the subjective amelioration obtained by autohemotherapy was more accentuated and lasting than with thyocyanate therapy, and moreover did not cause any of the disturbance which appear specially during the first days of treatment in the majority of the patients which receive thyocyanate. Only two patients had intolerance phenomena: benign erritrodernia which rapidly disappeared on withdrawal of the drug.

It is concluded that the administration of thyocyanate should be continued only when results comparable to those of group I are obtained or else, even if no reduction in blood pressure is obtained, when the amelioration of subjective symptoms is greater than that which can be attained by other therapeutic measures.

AUTHORS.

Wood, E. H., and Moe, G. K.: Blood Electrolyte Changes in the Heart-Lung Preparation With Special Reference to the Effects of Cardiac Glycosides. Am. J. Physiol. **137**: 6, 1942.

The effects of digitalis glycosides on blood electrolyte levels have been studied in 75 heart-lung preparations and in a number of control experiments. In some of these experiments whole blood potassium, glucose, cell volume, and serum sodium, calcium, and chloride analyses have also been carried out. These analyses and calculations based upon these analyses lead to the following conclusions: (1) In an untreated control heart-lung preparation a variable degree of hemo-concentration, a tendency for a slow increase in serum potassium, and a progressive fall of blood glucose occur. Constant changes in serum sodium, calcium, and chloride were not found. (2) Suitable doses of digitalis cause concomitant increases in external mechanical efficiency and blood and serum potassium along with a questionable decrease in serum potassium along with a questionable decrease in serum sodium. Significant differences from the untreated preparations were not demonstrated in the other blood components studied. (3) Therapeutic doses of digitalis glycosides produce relatively small but apparently significant increases in serum potassium. (4) A positive correlation was demonstrated between the total dose of a digitalis glycoside and the rate of serum potassium increase both during the efficiency increase period and for the duration of the drug's action. (5) The increased external efficiency and increased rate of potassium liberation which occur after suitable doses of digitalis are concomitant phenomena but a simple relationship between these two actions of digitalis on the heart-lung preparation is not evident. (6) Little if any correlation was found between the time of onset of digitalis irregularities and the rate of serum potassium increase or the potassium concentration of circulating serum. (7) The relative potassium mobilizing powers of the glycosides studied correspond somewhat more closely to their relative therapeutic activities than to their relative toxicities for the heart-lung preparation. (8) An increase in blood and serum potassium results from the action of suitable doses of digitalis glycosides in both the completely isolated heart and the completely isolated lung preparations. (9) The increased blood potassium resulting from digitalis action on the heart-lung preparation originates from both the heart and lung tissue.

AUTHORS.

Katz, L. N., Killian, S. T., Asher, R., and Perlow, S.: The Prophylactic Action of Desoxycorticosterone in Shock Due to Massive Venous Thrombosis. Am. J. Physiol. **137**: 79, 1942.

Experimental massive venous occlusion of a leg leads to a fall in blood pressure, a rise in hematocrit and an increase in the size of the leg amounting to 2.3 to 6.9 per cent of the body weight. This results in death in 3½ to from 12 to 21 hours. Only an occasional animal survives (2 out of 15 in our series).

The administration of desoxycorticosterone acetate (DCA) over a period of 24 hours previous to, and during the first 24 hours after the onset of the venous occlusion prevents the development of the state of shock and the animals survive (8 out of 11 in our series) despite a loss of fluid comparable to that in the control series.

When the DCA is not given sufficiently early before the onset of venous occlusion, the picture of shock and the mortality are similar to those of the untreated animals (death occurred in 8 out of 9). However, the average time of death is delayed somewhat and the loss of fluid is greater.

Evidence is given to show that DCA decreases the rate of fluid loss due presumably to some action on the oncotic pressure of the blood.

The action of DCA in preventing shock and the development of an irreversible state is due to some other mechanism in addition to its action on fluid loss from the blood. The nature of this action was not revealed by these studies.

AUTHORS.

Follis, R. H., Jr.: Myocardial Necroses in Rats on a Potassium Low Diet Prevented by Thiamine Deficiency. Bull. Johns Hopkins Hosp. **71**: 235, 1942.

The production of thiamine deficiency together with potassium deficiency in rats exerted a protective effect in these animals in that no myocardial necroses such as are seen in potassium deficiency developed. Possible explanations for this "protective" effect are considered.

Unlike observations in certain other species no cardiac changes were observed in rats on a thiamine deficient diet.

Changes in the kidneys characteristic of potassium deficiency did develop in all animals whether potassium alone or potassium together with thiamine was lacking.

In all but two of the sixteen potassium-thiamine deficient animals necroses of the voluntary muscle fibers were observed.

AUTHOR.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

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